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THE IMPACT OF SEROPOSITIVITY AND AGE ON LONG-TERM FOLLOW-UP DURATION IN RHEUMATOID ARTHRITIS

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Abstract:
Background and objectives: To investigate the predictive effects of demographic factors, acute phase reactants (ESR and CRP), serological markers (RF and Anti-CCP), and early biologic treatment strategies at diagnosis on the long-term follow-up duration at a tertiary referral center, from a ten-year perspective (2014-2024). **Materials and Methods:** This single-center, retrospective cohort study included 140 adult RA patients fulfilling the 2010 ACR/EULAR classification criteria. Baseline clinical characteristics, inflammatory, and autoimmune profiles of the patients were evaluated. The primary endpoint, long-term follow-up duration (months), was calculated based on the patients' first and last registry dates at the rheumatology outpatient clinic. The obtained data were analyzed using descriptive statistics, parametric/non-parametric comparison tests, and correlation analyses. **Results:** The study cohort, with a mean age of 63.18 ± 15.30 years, consisted of 66.4% female patients. Statistical analyses demonstrated that the mean follow-up duration of patients in the <65 age group (36.24 ± 42.37 months) was significantly longer compared to the ≥65 geriatric group (21.69 ± 30.82 months) ($p = 0.023$). Gender, geographical residence, and the use of biologic agents in the first year did not exert a significant impact on the follow-up duration. No statistical correlation was observed between baseline acute phase reactants (ESR and CRP levels) and cumulative follow-up duration. Conversely, the baseline serological profile was identified as a dramatic predictor of the follow-up period. The follow-up duration was profoundly longer in Rheumatoid Factor (RF) positive patients compared to negative ones (45.90

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months vs. 10.07 months; $p < 0.001$) and in Anti-CCP positive patients compared to negative ones (37.12 months vs. 22.67 months; $p = 0.024$). While the follow-up duration remained limited to an average of 8.59 months in patients negative for both autoantibodies, this duration increased to 43.02 months in patients positive for at least one autoantibody (composite seropositivity) ($p < 0.001$). **Conclusion:** In RA patients, the fundamental factor determining the need for long-term follow-up in a specialized rheumatology unit is the underlying autoimmune and serological phenotype of the disease, rather than the initial transient acute inflammatory burden. Seropositivity (RF and/or Anti-CCP) is a robust prognostic biomarker that guides clinical practice in identifying aggressive disease forms that require high-risk and persistent specialized care in long-term disease management.

Keywords: rheumatoid arthritis, seropositivity, rheumatoid factor, anti-CCP, follow-up duration, biomarkers

1. Introduction

Rheumatoid Arthritis (RA) is a systemic, chronic, and progressive autoimmune inflammatory disease with an incompletely elucidated etiology, emerging from a complex interplay between genetic susceptibility and environmental triggers. This pathological process, primarily targeting the synovial membrane, leads to cartilage destruction, marginal bone erosions, permanent joint deformities, and, consequently, a dramatic decline in the functional capacity and quality of life of patients when not managed with appropriate, effective, and timely interventions (1). Not limited to peripheral joints, RA is a multisystemic syndrome characterized by extra-articular manifestations such as cardiovascular system involvement, pulmonary complications in the form of interstitial lung disease (ILD), cutaneous symptoms like rheumatoid nodules, as well as ocular and neurological involvements (2).

Currently, the primary objective in RA management is the rapid suppression of inflammation to achieve and sustain clinical remission or, at the very least, low disease activity (LDA). According to the latest updated EULAR 2025 guidelines, the universal gold standard for the initial treatment of rheumatoid arthritis is the initiation of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), with methotrexate (MTX) acting as the "anchor" drug, often supported by short-term glucocorticoid bridging strategies (3). If an adequate response to these csDMARD strategies is not achieved within 3 to 6 months, biologic DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) must be integrated into the treatment algorithms (3).

The success of treatment strategies is objectively measured not only by short-term clinical responses but also by drug survival (retention rate) and the duration patients remain under active follow-up and treatment at a specialized referral center. In the literature, variables such as age, gender, disease duration, and baseline disease activity

are known to influence the clinical course (4,5). In particular, the presence of serological autoantibodies such as rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) highly correlates with radiological progression and poor prognosis (6,7). At the immunopathological level, specific HLA-DRB1 epitopes (the "shared epitope") and environmental stimuli like cigarette smoke lead to the modification of endogenous proteins through citrullination, setting the stage for chronic pro-inflammatory cytokine (TNF-α, IL-6, IL-1β) release and pannus formation, which accelerates joint destruction (1,5).

Specifically, RF and Anti-CCP positivity are not only diagnostic tools but also robust prognostic biomarkers closely associated with joint erosion and disease severity (6,7). This immunopathological severity complicates patients' response to treatment, potentially necessitating higher doses of medications and statistically prolonging follow-up periods (7). However, in the modern treatment era, there remains a need for long-term registry data regarding how these serological and demographic parameters impact the duration patients remain under care in a tertiary healthcare facility in real-world settings. The aim of this study is to investigate the effects of age of onset, gender, place of residence, baseline acute phase reactants (ESR and CRP), serological markers (RF and anti-CCP), and the initiation of biologic agents within the first year of treatment on the total long-term follow-up duration in RA patients followed over a 10-year period (2014-2024).

2. Material and Methods

2.1 Study Design and Ethics Committee

This research was designed as a single-center, retrospective cohort study. The study protocol was approved by the Ondokuz Mayis University Clinical Research Ethics Committee (Decision No: 2024/347, Date: 28.08.2024) and was conducted in accordance with the principles of the Declaration of Helsinki.

2.2 Patient Selection and Study Population

Patients aged 18 years and older who applied to the Ondokuz Mayis University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology outpatient clinic between 2014 and 2024, and received a definitive RA diagnosis according to the 2010 ACR/EULAR Classification Criteria (8), were included in the study. Patients followed by Physical Medicine and Rehabilitation (PMR) clinics (to prevent heterogeneity in follow-up and treatment standards), patients under 18 years of age, and patients with missing critical clinical/laboratory data in their medical records (n = 20) were excluded. Final statistical analyses were conducted on 140 patients.

2.3 Clinical Data Collection and Variables

Patients' electronic medical record systems were reviewed, and demographic data (age, gender, place of residence), baseline laboratory parameters at the time of diagnosis (ESR,

CRP, RF, anti-CCP), dates of the first and last outpatient clinic visits, and applied treatment strategies (whether a transition to a biologic agent occurred within the first year) were recorded on standardized forms. The long-term follow-up duration at the tertiary specialized center was determined by calculating the difference, in months, between the patient's first and last registry dates at the outpatient clinic.

2.4 Laboratory Measurements and Analyses

Baseline laboratory parameters were analyzed according to the standard protocols of the Ondokuz Mayis University Faculty of Medicine Central Laboratory. Erythrocyte Sedimentation Rate (ESR) was measured using the Westergren method in mm/hour; C-Reactive Protein (CRP) levels were measured using an immuno-turbidimetric method in mg/L. Rheumatoid Factor (RF) positivity was determined by the nephelometric method, with values of 15 IU/mL and above considered positive. Anti-Citrullinated Peptide (Anti-CCP) antibody levels were analyzed using the chemiluminescent microparticle immunoassay (CMIA) method, and values of 17 U/mL and above were defined as the positivity threshold.

2.5 Statistical Analysis

SPSS v21.0 (IBM Corp., Armonk, NY, USA) software was used for data analysis. The demographic characteristics and clinical parameters of the participants were evaluated using descriptive statistics. The conformity of numerical data to normal distribution was examined using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Continuous data fitting a normal distribution were presented as mean ± standard deviation (SD), while non-normally distributed data were presented as median and interquartile range (IQR). Categorical variables were expressed as numbers (n) and percentages (%).

Differences in follow-up duration between two independent, normally distributed groups were analyzed using the Independent Samples t-test, whereas non-normally distributed data were analyzed using the Mann-Whitney U test. The One-Way ANOVA test was applied for the comparison of more than two independent groups. Pearson Chi-Square test and, when necessary, Fisher's Exact Test were used for the comparison of proportions of categorical variables. The strength and direction of the relationship between baseline inflammatory parameters (ESR and CRP) and follow-up duration were examined using the Spearman rank correlation coefficient (ϱ). Multivariate models (Cox regression or multiple linear regression) were not established to minimize the risk of Type II error due to retrospective database limitations and the small sample size in the early biologic agent arm; primary predictors were defined using univariate analyses. A p-value of < 0.05 was considered statistically significant for all analyses.

3. Results

3.1 Characteristics of the Study Population

The demographic, clinical, and baseline laboratory characteristics of the 140 RA patients included in the study are presented in Table 1. The mean age of the cohort was 63.18 ± 15.30 years, and the patients consisted of 66.4% females (n = 93) and 33.6% males (n = 47). Of the patients, 48.6% (n = 68) were under 65 years of age, while 51.4% (n = 72) were 65 years of age and older. Regarding geographical distribution, 45.7% (n = 64) of the patients resided in Samsun, 8.6% (n = 12) in Sinop, and 45.7% (n = 64) applied from other surrounding provinces.

The mean ESR level at the time of diagnosis was 45.31 ± 29.09 mm/hour, and the CRP level was 25.08 ± 40.73 mg/L. When the serological profile was examined, RF positivity was present in 52.1% (n = 73) of the patients, and Anti-CCP positivity was present in 57.8% (n = 81); the composite seropositive group, positive for at least one autoantibody, constituted 58.6% (n = 82) of the cohort. The rate of initiation of a biologic agent during the first year of follow-up was recorded as 6.4% (n = 9).

Table 1: Baseline Demographic and Clinical Characteristics of the Study Cohort

Parameter Characteristics	**Cohort Distribution [n (%) or Mean ± SD]**
Age (Years), Mean ± SD	63.18 ± 15.30
Age Groups, n (%)	
< 65 Years	68 (48.6%)
≥ 65 Years	72 (51.4%)
Gender, n (%)	
Female	93 (66.4%)
Male	47 (33.6%)
Place of Residence, n (%)	
Samsun	64 (45.7%)
Sinop	12 (8.6%)
Other Provinces	64 (45.7%)
Inflammatory Biomarkers	
Baseline ESR (mm/hour)	45.31 ± 29.09
Baseline CRP (mg/L)	25.08 ± 40.73
Serological Profile, n (%)	
RF Positivity	73 (52.1%)
Anti-CCP Positivity	81 (57.8%)
Composite Seropositivity (RF and/or Anti-CCP)	82 (58.6%)
Treatment Strategy in the 1st Year, n (%)	
Receiving Biologic Agents	9 (6.4%)
Receiving Only csDMARDs	131 (93.6%)

***Note:** Abbreviations: ESR, Erythrocyte Sedimentation Rate; CRP, C-Reactive Protein; RF, Rheumatoid Factor; Anti-CCP, Anti-Cyclic Citrullinated Peptide Antibody; csDMARD, Conventional Synthetic Disease-Modifying Antirheumatic Drug; SD, Standard Deviation.

3.2 Factors Affecting Follow-Up Duration

The results of the univariate analyses of the effects of various clinical, demographic, and serological variables on the duration of hospital follow-up are detailed in Table 2.

In the comparison between age groups, the mean follow-up duration of the younger patient group under 65 years of age (36.24 ± 42.37 months) was found to be statistically significantly longer compared to the geriatric group aged 65 and over (21.69 ± 30.82 months) ($p = 0.023$). However, gender (female: 27.96 ± 36.46 months vs. male: 30.34 ± 39.75 months, $p = 0.731$) and place of residence (Samsun: 33.16 ± 40.90 months, Sinop: 15.75 ± 29.05 months, Other: 28.64 ± 34.96 months, $p = 0.288$) did not have a determinant effect on follow-up durations.

When analyzing the relationship between serological status and follow-up duration, the follow-up duration of RF-positive patients (45.90 ± 44.61 months) was highly significantly longer than that of RF-negative patients (10.07 ± 10.31 months) ($p < 0.001$). Similarly, the mean follow-up duration in the Anti-CCP positive group (37.12 ± 40.49 months) was significantly higher compared to the negative group (22.67 ± 34.08 months) ($p = 0.024$). While the follow-up duration in the group negative for both RF and Anti-CCP was limited to only 8.59 ± 9.13 months, this duration dramatically increased to 43.02 ± 43.05 months in the group with at least one seropositivity (composite seropositivity) ($p < 0.001$).

No statistically significant relationship was found between the initiation of a biologic agent within the first year after diagnosis and follow-up duration (early biologics: 27.67 ± 27.39 months vs. csDMARDs: 28.83 ± 38.14 months, $p = 0.928$).

Table 2: The Impact of Demographic, Clinical, and Serological Factors on Follow-Up Duration in a Specialized Center

Variables	Categories	n	Mean Follow-up Duration (Months) ± SD	p-value
Age Group	< 65 Years	68	36.24 ± 42.37	0.023*
	≥ 65 Years	72	21.69 ± 30.82	
Gender	Female	93	27.96 ± 36.46	0.731
	Male	47	30.34 ± 39.75	
Place of Residence	Samsun	64	33.16 ± 40.90	0.288
	Sinop	12	15.75 ± 29.05	
	Other Provinces	64	28.64 ± 34.96	
RF Status	Negative	67	10.07 ± 10.31	< 0.001*
	Positive	73	45.90 ± 44.61	
Anti-CCP Status	Negative	59	22.67 ± 34.08	0.024*
	Positive	81	37.12 ± 40.49	
Composite Seropositivity	Both Negative	58	8.59 ± 9.13	< 0.001*
	At Least One Positive	82	43.02 ± 43.05	
Biologics in 1st Year	Not Receiving	131	28.83 ± 38.14	0.928
	Receiving	9	27.67 ± 27.39	

Note: In statistical comparisons, parametric tests (t-test, ANOVA) were used for normally distributed variables, and non-parametric tests (Mann-Whitney U) for non-normally distributed ones. The significance threshold was set at $p < 0.05$.

3.3 Distribution of Serological and Clinical Characteristics by Gender

Analyses conducted to examine the relationship between gender and serological profile (RF positivity, Anti-CCP positivity, composite positivity), place of residence, and rates of initiating aggressive biologic treatment in the first year revealed no statistically significant heterogeneity between the groups (Table 3). RF positivity was similar between females (50.5%) and males (55.3%) ($p = 0.593$). The rates of initiating a biologic agent within the first year were 6.5% for female patients and 6.4% for male patients, demonstrating clinical similarity ($p = 0.988$).

Table 3: Comparison of Serological and Clinical Characteristics by Gender

Clinical / Serological Variables	Female (n=93)	Male (n=47)	p-value
RF Positivity, n (%)	47 (50.5%)	26 (55.3%)	0.593
Anti-CCP Positivity, n (%)	57 (61.3%)	24 (51.1%)	0.247
Composite Seropositivity, n (%)	53 (56.9%)	29 (61.7%)	0.539
Biologic Treatment in 1st Year, n (%)	6 (6.5%)	3 (6.4%)	0.988
Distribution of Residence, n (%)			
- Samsun	42 (45.2%)	22 (46.8%)	0.982
- Sinop	8 (8.6%)	4 (8.5%)	
- Other Provinces	43 (46.2%)	21 (44.7%)	

Note: Pearson Chi-Square and Fisher's Exact tests were used in statistical comparisons. A level of $p < 0.05$ was considered significant.

3.4 Relationship Between Baseline Inflammatory Parameters and Follow-Up Duration

In the Spearman correlation analysis performed to evaluate the predictive power of acute phase reactants measured at diagnosis on cumulative clinical follow-up durations, it was shown that neither baseline sedimentation rate ($\varrho = -0.112$, $p = 0.186$) nor baseline CRP levels ($\varrho = -0.134$, $p = 0.113$) exhibited a statistically significant correlation with follow-up duration (Table 4).

Table 4: Relationship Between Baseline Acute Phase Reactants and Total Follow-Up Duration

Biomarker Parameter	Mean ± SD	Correlation Coefficient (Spearman ϱ)	p-value
Baseline ESR (mm/hour)	45.31 ± 29.09	-0.112	0.186
Baseline CRP (mg/L)	25.08 ± 40.73	-0.134	0.113

Note: Spearman Rank Correlation Coefficient (ϱ) was used in the correlation analysis. A level of $p < 0.05$ was considered significant. Abbreviations: ESR, Erythrocyte Sedimentation Rate; CRP, C-Reactive Protein.

4. Discussion

Rheumatoid arthritis (RA) is a chronic inflammatory disease that exhibits significant heterogeneity regarding its clinical course and treatment response. This 10-year retrospective cohort study evaluated the factors influencing long-term follow-up duration among RA patients managed at a tertiary rheumatology center. The primary finding of our study is that the baseline serological profile plays a more robust role in predicting long-term follow-up duration than acute inflammation markers. While RF positivity, Anti-CCP positivity, and notably composite seropositivity were significantly

associated with longer follow-up durations, no significant relationship was observed between baseline ESR and CRP levels and follow-up time. Furthermore, it was demonstrated that patients under 65 years of age had longer follow-up durations.

The most striking outcome of our study is the strong association between serological status and follow-up duration. While the mean follow-up duration for patients negative for both RF and Anti-CCP was only 8.59 months, this duration reached 43.02 months for patients positive for at least one autoantibody. In other words, seropositive patients were followed at the tertiary rheumatology center for approximately five times longer. This finding aligns with previous studies indicating that RF and Anti-CCP positivity are associated with a more aggressive disease course, faster radiological progression, and a higher risk of functional loss (9–11). It is particularly well-known that Anti-CCP antibodies contribute to bone destruction by increasing osteoclast activation, and a high autoantibody burden is associated with a more refractory disease course (12). Therefore, it is expected that seropositive patients necessitate more frequent treatment modifications and require prolonged specialized rheumatology care.

Another notable finding is that the impact of RF positivity on follow-up duration appeared more pronounced than that of Anti-CCP positivity. While the mean follow-up duration in RF-positive patients was approximately 46 months, it was only 10 months in RF-negative patients. In contrast, the difference associated with Anti-CCP positivity was more limited. Although most studies in the literature report Anti-CCP as a stronger marker for radiological progression and poor prognosis (9–11), some real-world cohorts have demonstrated that RF levels exert significant effects on treatment response and drug survival (13). The results of our study suggest that in daily clinical practice, RF positivity may still be an important determinant of the need for specialized follow-up.

Perhaps the most crucial conceptual contribution of our study is the failure of biomarkers reflecting baseline inflammation to predict long-term follow-up duration. Although ESR and CRP levels have been fundamental parameters for evaluating disease activity for years, their significant impact on long-term follow-up duration could not be demonstrated in our study. This situation may stem from the fact that while acute-phase reactants indicate the inflammatory burden of the disease at a specific moment, they do not reflect the underlying immunological phenotype. Today, rheumatoid arthritis is widely acknowledged as a heterogeneous disease comprising different biological subtypes (14). Hence, it seems more probable that the determinant of the long-term clinical course is the immunological character of the disease rather than transient inflammatory activity. Indeed, recently published studies have revealed the existence of RA phenotypes that, despite normal or low CRP levels, exhibit a progressive course and can develop severe structural damage (15). Furthermore, in a study by Saptarini et al., no significant relationship could be demonstrated between ESR and disease duration (16). Taken together, these findings suggest that the serological phenotype holds stronger prognostic value than inflammatory markers in determining the need for long-term specialized care.

Age was also found to be a significant variable influencing follow-up duration. The follow-up durations of patients under sixty-five years of age were significantly longer compared to the older age group. There may be several explanations for this. Younger patients have a longer life expectancy and harbor higher expectations regarding the prevention of workforce loss and the maintenance of functional capacity. Therefore, treatment targets are set more aggressively, and specialized follow-up is maintained for a longer period. Moreover, some studies have reported that young-onset RA is associated with more intense immunological activity (17). Conversely, an increase in the comorbid disease burden, elevated risks of infection and drug toxicity, and more conservative treatment goals in the elderly population can shorten the follow-up duration. Real-world biologic treatment registries have also shown that advanced age is associated with shorter drug survival and higher treatment discontinuation rates (4,17,18).

It is also noteworthy that gender did not have a significant effect on follow-up duration in our study. Even though RA is more common in women, no difference was observed between female and male patients regarding the need for long-term specialized follow-up. This result is consistent with studies reporting that gender has no significant effect on treatment continuity and retention in care among patients receiving biologic therapies (19). Similarly, the lack of a significant effect of the province of residence on follow-up duration suggests that access to healthcare services and the referral system are relatively homogeneous in the region where the study was conducted.

The finding that the initiation of a biologic agent within the first year after diagnosis did not affect the follow-up duration is also interesting. However, this result should be interpreted with caution due to the very small number of patients using biologic agents. Additionally, since biologic treatments are predominantly used in more severe and treatment-resistant cases, confounding by indication for this variable is inevitable. International registry systems have demonstrated that serological status is one of the most crucial factors determining drug survival in patients receiving biologic treatments [9,10]. Thus, the impact of biologic therapies on long-term follow-up requires re-evaluation in studies with larger sample sizes.

This study has several limitations. Its retrospective and single-center design limits the generalizability of the findings. Furthermore, potential confounding variables such as smoking history, disease activity scores, the extent of radiological damage, and comorbidity burden could not be evaluated. The statistical power of subgroup analyses was also limited by the low number of patients on biologic treatments. Nevertheless, our study's reliance on 10 years of real-world data and its demonstration of a robust relationship between serological status and long-term follow-up can be considered significant strengths.

5. Conclusion

In conclusion, this study demonstrates that the fundamental factor determining the need for long-term specialized rheumatology follow-up in rheumatoid arthritis is the

serological and immunological character of the disease, rather than the initial level of inflammation. In particular, patients with RF and/or Anti-CCP positivity can be considered a high-risk subgroup requiring prolonged specialized care. Our findings underscore the importance of serological markers in the development of personalized follow-up strategies for rheumatoid arthritis and support the value of immunological phenotyping in long-term clinical management.

Conflict of Interest Statement
The authors declare no conflicts of interest.

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