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ORIGINAL ARTICLE

The first involved joints and associated factors in patients with rheumatoid arthritis

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ABSTRACT

Objectives: This study aimed to investigate the first involved joints and associated factors in Turkish patients with rheumatoid arthritis (RA).

Patients and methods: This retrospective cross-sectional study included 300 newly diagnosed and disease-modifying antirheumatic drug-naïve RA patients (240 females, 60 males; mean age: 54±1.2 years; range, 18 to 82 years). Baseline demographic, clinical, and laboratory data were evaluated between January 2022 and December 2022. The patients were divided into four groups according to autoantibody profile: antibody-negative patients (Group 1; both RF and anti-CCP were negative in this group of patients), RF-positive patients (Group 2), anti-CCP-positive patients (Group 3), and patients with dual seropositivity with RF and anti-CCP (Group 4). The patients were also divided into two groups according to the size of the first affected joint: patients with SJI at diagnosis and patients without SJI involvement at diagnosis.

Results: Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP) antibody positivity rates were 40.3% and 35.6%, respectively. The mean lag time to diagnosis was 25±36 months. At the disease onset, 20% of patients did not have small joint involvement (SJI). Seronegative patients tended to be female (p=0.001), had longer lag time (p=0.001), and had lower levels of C-reactive protein (p=0.025), white blood count (p=0.005), and neutrophil/lymphocyte ratio (p=0.001) compared to the dual seropositive group. Patients presenting with SJI had a younger age (p=0.002), tended to be female (p=0.001), and had lower RF (p=0.034) and anti-CCP (p=0.031) positivity. Only age (p=0.005) and dual seronegativity (RF and anti-CCP; p=0.035) were the independent predictors of SJI in multivariate analysis.

Conclusion: The decreasing age and seronegative status were defined as independent risk factors of SJI at the onset of RA. Population-based, prospective studies are needed for earlier diagnosis.

Keywords: Auto-antibodies, early rheumatoid arthritis, rheumatoid arthritis, risk factor, small joint.

Rheumatoid arthritis (RA) is a chronic, autoimmune, progressive, and multisystemic inflammatory disease affecting 0.5 to 1% of the white population. The cause of RA is unknown; multiple genetic and environmental risk factors are associated with pathogenesis. Synovial joints are the main target tissue and chronic erosive arthritis usually occurs.[1] Reduction in work capacity and excess mortality is the natural consequences of RA.[2] Early diagnosis and early treatment are associated with reduced joint damage, extra-articular manifestations, and better prognosis.[3,4] Therefore, early treatment is the cornerstone of the European Alliance of Associations for Rheumatology (EULAR) treatment guidelines for RA.[5,6] The 1987 American College of Rheumatology (ACR) RA classification criteria[7] provide good sensitivity for the established disease but not early RA.[8] Thus, the 2010 ACR/EULAR RA classification criteria[9] were developed, which are more useful for detecting early RA than the 1987 ACR criteria.[10]

Rheumatoid arthritis usually insidiously starts from small joints of hands and feet as symmetric polyarthritis.[11] Large joint involvement (LJI), such as the hip or knee joints, is not common in the early stage[12] and is a sign of the established stage.[13] Therefore, the clinical assessment of the 2010 ACR/EULAR classification criteria is mainly based on polyarticular involvement of small

joints of hands, such as the metacarpophalangeal and proximal interphalangeal joints, classifying patients as RA in earlier stages; large joints have less potency in this scoring system. Therefore, the recent 2010 ACR/EULAR classification criteria can lack sensitivity to detect recent-onset patients with RA who present with LJI. This can lead to prolonged lag time for diagnosis and joint deformities in patients with RA who have large joint arthritis at the disease onset. Furthermore, LJI in the early stages of RA is associated with radiographic damage of hands and feet, disease activity, and physical disability.[14]

Whether there are any differences in baseline characteristics between patients with RA presenting with small joint involvement (SJI) or LJI is unclear. The patients that present with LJI could be another subtype of RA. Whether the autoantibody profile has an effect on the onset of RA is also in consideration. Hence, this study aimed to investigate these issues since previous studies generally defined the clinical presentation and did not focus on the first involved joint. Moreover, joint distribution, autoantibody profile, including rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP) antibody, acute phase responses, including erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) present in the 2010 ACR/EULAR classification criteria and vary across countries at the onset of RA.[15] Thus, it is crucial to define the population-based characteristics. However, there is no existing data about the baseline parameters in our population. Therefore, we attempted to define the baseline characteristics of RA, which could have a prognostic value for early diagnosis in the Turkish population.

PATIENTS AND METHODS

In this retrospective cross-sectional study, 300 RA patients (240 females, 60 males; mean age: 54±1.2 years; range, 18 to 82 years) who were newly diagnosed between January 2022 and December 2022 (during one year) at the tertiary rheumatology department of the Hatay Mustafa Kemal University Hospital were analyzed. Patients' electronic files were reviewed; demographic, clinical, and laboratory data were noted. The inclusion criteria were being aged 18 years or older, fulfilling the 2010 ACR/EULAR RA classification criteria,[9] and being diagnosed as RA for the first time. Patients receiving glucocorticoids or conventional synthetic or targeted synthetic/biologic disease-modifying antirheumatic drugs (DMARDs) before referral to our clinic and those who had any cause of arthritis (rheumatic or nonrheumatic, such as reactive arthritis, crystal arthritis, osteoarthritis, septic arthritis, traumatic arthritis, and paraneoplastic arthritis) were excluded.

At the initial visit, the patient's history was carefully taken. A physical examination and standard laboratory tests were performed. Laboratory tests were obtained at the time of diagnosis by our rheumatology department. First affected joints, smoking history (active or previous), and comorbidities were noted. Chronic kidney disease was defined as a glomerular filtration rate <60 mL/min/1.73 m^2 lasting longer than three months. Diagnosis of coronary artery disease was based on only conventional angiography. The first arthritic joint was determined by asking patients and defined as a combination of swelling, pain, and morning stiffness in a peripheral joint; these questionnaires have 86 to 90% sensitivity and 90% specificity. Hip involvement was confirmed by magnetic resonance imaging. Lag time was defined as the time between first arthritis occurring time and diagnosis as RA. The diagnosis of Sjögren's syndrome (SjS) was defined according to the 2016 ACR/EULAR classification criteria.[16]

Autoantibodies, ESR, CRP, and complete blood count were assessed from serum samples. Total leucocyte count and subtypes were analyzed using an automated blood cell counter. The neutrophil/lymphocyte ratio (NLR) was defined as a simple ratio between the absolute neutrophil and absolute lymphocyte counts and derived from the complete blood count. A nephelometric assay was used to determine RF (immunoglobulin M subtype), and a value ≥15 IU/mL was defined as positive. Anti-CCP antibody (immunoglobulin G subtype) was determined by enzyme-linked immunosorbent assay, and a value ≥5 U/mL was defined as positive. The patients were divided into four groups according to autoantibody profile: antibody-negative patients (Group 1; both RF and anti-CCP were negative in this group of patients), RF-positive patients (Group 2), anti-CCP-positive patients (Group 3), and patients with dual

seropositivity with RF and anti-CCP (Group 4). The patients were also divided into two groups according to the size of the first affected joint: patients with SJI at diagnosis (SJI group) and patients without SJI involvement at diagnosis (non-SJI group). ESR was determined by the Westerngren method, and a value >20 mm/h was defined as a high value. CRP was determined by nephelometric assay, and a value >5 mg/L was described as a high value. If a patient had an active infectious disease, such as urinary tract or pulmonary system, at the time of diagnosis, CRP was measured after treating the infection. Anemia was defined as a serum hemoglobin level <12 g/dL in females and <13 g/dL in males. Other possible causes of anemia, such as iron deficiency, were also excluded.

Plain radiographs of the wrist, hands, feet, and affected joints were performed at the first visit. Radiographs were assessed by rheumatologists. If there was any disagreement between assessors, X-rays were reread, then the final decision was made with full agreement between assessors. The definition of joint erosion was based on the 2010 ACR/EULAR criteria.[17] Typical joint involvement (TJI) was defined as having any erosion or joint space narrowing according to the Modified Sharp Score.[18] According to the Modified Sharp Score, severe joint erosion was defined as having an erosion or joint space narrowing ≥50% in any joint. Small or large joints were classified according to the 2010 ACR/EULAR RA criteria.[9] The shoulder, elbow, hip, knee, and ankle were classified as large joints; metacarpophalangeal, proximal interphalangeal (PIP), second through fifth metatarsophalangeal, and interphalangeal joints and the wrist were classified as small joints. The distal interphalangeal joints, first metatarsophalangeal joints, and first carpometacarpal joint involvement were excluded.

Statistical analysis

Data were analyzed using IBM SPSS version 26.0 software (IBM Corp., Armonk, NY, USA). The normality of continuous variables was evaluated with the Shapiro-Wilk and Kolmogorov-Smirnov tests. Nonparametric statistical methods were applied for values with skewed distribution. Descriptive statistics were presented as the mean ± standard deviation (SD) for normally distributed variables and the median (25^{th}-75^{th} percentiles) for nonnormally distributed variables. Kruskal-Wallis test was used to compare more than two variables that were nonnormally distributed, and Dunn's multiple comparison tests were used for post hoc pairwise multiple comparison analyses. One-way analysis of variance was used to compare more than two normally distributed groups, and Tukey's test was used for post hoc pairwise multiple comparison analysis. The chi-square test was used to analyze the relationships between categorical variables. Significance values were adjusted with Bonferroni correction for multiple tests. A binary logistic regression model was conducted to evaluate the risk ratios of patients with and without SJI. The model was adjusted for age, sex, and autoantibody profile. A p-value <0.05 was considered statistically significant.

RESULTS

The lag time to diagnosis was a mean of 25±36 months. A smoking history was present in 36.3%, and the most common comorbidity was hypertension (25.6%). RF and anti-CCP positivity were 40.3% and 35.6%, respectively. Nearly half of the patients (n=148) existed in Group 1. TJI was observed in 94% of patients, and 6% had severe joint erosion. Elevated ESR and CRP were observed in 40.3% and 50% of patients, respectively; 60.3% (n=181) of patients had a high value of ESR or CRP. The anemia rate was 26%. The most common first affected joint was the hand/wrist (40%), and the rarest was the hip (0.3%). Two hundred nineteen (73%) patients had SJI; 81 (27%) had no SJI at the onset of the disease. Table 1 shows baseline demographic, laboratory, and clinical characteristics. Patients presenting with SJI and SJI + knee arthritis (n=240) had classically insidious polyarticular onset. Patients with shoulder, elbow, knee, ankle, and temporomandibular arthritis (n=59) had palindromic onset; only one patient with hip involvement had chronic monoarticular onset (n=1). At the time of diagnosis, non-SJI patients with TJI on X-ray developed polyarticular disease during follow-up. Only one patient with shoulder involvement (RFi 19I U/mL; anti-CCP, 201 U/mL) did not have TJI. This patient also had a very short disease duration of two months.

Table 1. Demographic, laboratory, and clinical characteristics of patients at the first visit (n=300)

	n	%	Mean±SD	Min-Max
Age (year)			54±1.2	18-82
Sex				
Female	240	80		
Male	60	20		
Disease duration time (year)			2.1	
Lag time (month)			25.3	
Smoking (active or ex)	109	36.3		
Comorbidities				
Hypertension	77	25.6		
Diabetes mellitus	57	19		
Coronary artery disease	31	10.3		
Chronic kidney disease	6	2		
Secondary Sjögren's syndrome	9	3		
RF positivity	121	40.3		
RF titer (IU/mL)			154	15-2830
RF =15-45 IU/mL	45	37.2		
RF ≥45 IU/mL	76	62.8		
Anti-CCP positivity	107	35.6		
Anti-CCP titer (U/mL)			99	5-452
Anti-CCP =5-15 U/mL	31	29		
Anti-CCP ≥15 U/mL	76	71		
Auto-antibody profile				
Group 1: RF–/anti-CCP–	148	49.3		
Group 2: RF+/anti-CCP–	45	15		
Group 3: RF–/anti-CCP+	31	10.3		
Group 4: RF+/anti-CCP+	76	25.3		
Typical joint involvement	282	94		
Serious joint erosive	18	6		
ESR (mm/h)			20	2-87
ESR (>20 mm/h)	121	40.3		
CRP (mg/L)			12	1-139
CRP (>5 mg/L)	152	50.6		
WBC (/mm^3)			8330	3650-17250
WBC (>10000/mm^3)	67	22.3		
Neutrophil (/mm^3)			5225	1560-12830
Neutrophil (>7500/mm^3)	41	13.6		
Lymphocyte (/mm^3)			2380	630-5480
Neutrophil/Lymphocyte ratio			2.2	
Hemoglobin (g/dL)			13	9.0-17.9
Anemia	78	26		
Platelet count (/mm^3)			303	115-661
Platelet count (>450000/mm^3)	12	4		
First involved joint at the disease onset				
Hand/wrist	120	40		
Foot	27	9		
Hand/wrist + foot	72	24		
Knee	32	10.7		
Hand/wrist + foot + knee (mix type)	21	7		
Shoulder	10	3.3		
Elbow	6	2		
Temporomandibular	2	0.7		
Hip	1	0.3		
Ankle	9	3		
Patients presenting with only SJI	219	73		
Patients presenting with LJI	81	27		

RF: Rheumatoid factor; anti-CCP: Anti-cyclic citrullinated peptid antibody; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; WBC: White blood count; SJI: Small joint involvement; LJI: Large joint involvement.

Table 2 demonstrates the baseline characteristics of the patients according to antibody profile. There were 148 (49%) patients in Group 1, 31 (10%) in Group 2, 45 (15%) in Group 3, and 76 (26%) in Group 4. Seronegative patients tended to be female more than dual seropositive patients (87.2% *vs.* 65.8%, respectively; p=0.001). The four groups were similar regarding smoking history, TJI, ESR, hemoglobin levels, and platelet counts. CRP (p=0.025), white blood count (WBC; p=0.005), and NLR (p=0.001) were lower in Group 1 [5 (1-12.5), 7840 (6290-9070), 2 (1.5-2.5), respectively] than in Group 4 [9 (4-19), 8880 (7105-10665), 2.55 (1.80-3.30), respectively]. Group 4 had a shorter median lag time of 5 months than Group 1's 12 months (p=0.001). There was no discernible difference in the type of joints between the four groups.

Characteristics of subjects according to the size of involved joint involvement are shown in Table 3. Patients in the SJI group were more often female than in the non-SJI group (84.5% *vs.* 67.9%, respectively; p=0.001). Subjects of the SJI group were younger than those of the non-SJI group (49.7±11.6 *vs.* 54.6±12.1, respectively; p=0.002). Smoking history, lag time, TJI, inflammatory markers (ESR, CRP, WBC, and NLR), hemoglobin, platelet counts, RF titer, and anti-CCP titer were similar between the two groups. However, RF positivity (36.5% *vs.* 50.6%, p=0.034) and anti-CCP positivity (32% *vs.* 45.7%, p=0.031) rates were lower in the SJI group than in the non-SJI group. In the binary logistic regression model (adjusted for sex and antibody status), the baseline age was independently predictive for SJI [odds ratio (OR)=1.035, 95% confidence interval (CI): 1.010-1.060, p=0.005). Considering potential confounders, seronegative patients were more likely to have SJI than dual seropositive patients (OR=0.494, 95% CI: 0.257-0.951, p=0.035).

DISCUSSION

In the literature, this study constitutes a novel definition of the first involved joints in patients with RA. The findings demonstrate female sex predominance, shorter lag time, and higher inflammatory markers, such as CRP, WBC,

Table 2. Comparison of patients' characteristics according to auto-antibody profile

	Group 1 (n=148)	Group 2 (n=45)	Group 3 (n=31)	Group 4 (n=76)	*p*
Age (year) median (25^{th}-75^{th} percentils)	52.5 (43-59.5)	53 (43-61)	50 (41-56)	50 (41.5-57.5)	>0.05
Sex n, (%)					
Female	129 (87.2)	39 (86.7)	22 (71)	50 (65.8)†	**0.001**
Lag time (months) median (25^{th}-75^{th} percentils)	12 (6-36)	12 (6-36)	12 (5-36)	5 (2-13)†	**0.001**
Smoking, n, (%)	99 (66.9)	34 (75.6)	16 (51.6)	42 (55.3)	>0.05
Typical joint involvement, n, (%)	138 (93.2)	43 (95.6)	28 (90.3)	73 (96.1)	>0.05
ESR (mm/h) median (25^{th}-75^{th} percentils)	16 (9-26.5)	17 (7-31)	21 (11-31)	18 (10.5-26)	>0.05
CRP (mg/L) median (25^{th}-75^{th} percentils)	5 (1-12.5)	5 (1-11)	4 (1-17)	9 (4-19)†	**0.025**
WBC (cells/μL) median (25^{th}-75^{th} percentils)	7840 (6290-9070)	7670 (6600-9100)	7360 (6620-8940)	8880 (7105-10665)†	**0.005**
Hemoglobin (g/dL) mean±SD	12.9±1.28	12.89±1.65	12.85±1.92	13.15±1.68	>0.05
Platelet (10^3/μL) median (25^{th}-75^{th} percentils)	292 (250-333.5)	284 (212-350)	310 (251-348)	311.5 (252.5-364.5)	>0.05
NLR, median (25^{th}-75^{th} percentils)	2 (1.5-2.5)	2 (1.6-2.8)	2.2 (1.6-3.7)	2.55 (1.80-3.30)†	**0.001**
SJI, n, (%)	118 (79.7)	31 (68.9)	21 (67.7)	49 (64.5)	>0.05
LJI, n, (%)	21 (14.2)	12 (26.7)	8 (25.8)	19 (25)	>0.05

ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; WBC: White blood count; SD: Standard deviation; NLR: Neutrophil/ lymphosit ratio; SJI: Small joint involvement; LJI: Large joint involvement. Statistically significant at p<0.05; † p<0.0125 versus group 1. Significance values adjusted by the Bonferroni correction for multiple tests. Group 1: Seronegative patients, Group 2: RF+/anti-CCP- patients, Group 3: RF-/anti-CCP+ patients, Group 4: Dual antibody positive patients. Numbers in bold type indicate statistically significant differences.

Table 3. Comparison of patient characteristics according to joint involvement

	SJI (n=219)					Non-SJI (n=81)					
	n	%	Mean±SD	Median	25th-75th percentiles	n	%	Mean±SD	Median	25th-75th percentiles	*p*
Age (year)			49.7±11.6					54.6±12.1			**0.002**
Sex Female	185	84.5				55	67.9				**0.001**
Lag time (month)				12	4-36				12	4-36	>0.05
Smoking	79	36.1				30	37				>0.05
Typical joint involvement	205	93.6				77	95.1				>0.05
RF positivity	80	36.5				41	50.6				**0.034**
RF titer (IU/mL)				74	36-165.5				83	30-155	>0.05
Anti-CCP positivity	70	32				37	45.7				**0.031**
Anti-CCP titer (U/mL)				79	14-198				48	10-201	>0.05
ESR (mm/h)			20.5±14.8					19.7±16.3			>0.05
CRP (mg/L)				5	1-13				6	1-15	>0.05
WBC (cells/μL)			8321±2506					8359±2421			>0.05
Hemoglobin (g/dL)				13	12-13.9				13.2	12.2-13.9	>0.05
Platelet count (10^3/μL)			303±81					305±100			>0.05
NLR				2.1	1.6-2.8				2.2	1.8-3	>0.05

SJI: Small joint involvement; SD: Standard deviation; RF: Rheumatoid factor; anti-CCP: Anti-cyclic citrullinated peptid antibody; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; WBC: White blood count: NLR: Neutrophil/lymphosit ratio; Numbers in bold type indicate statistically significant differences.

and NLR, in patients with dual seropositivity compared to seronegative patients. Additionally, patients presenting with no SJI had significantly higher age, female sex ratio, RF positivity, and anti-CCP positivity than those presenting with SJI; baseline age and seronegative profile were the independent predictors of SJI in patients with RA. Baseline demographic, laboratory, and clinical characteristics of DMARD-naïve Turkish patients with RA who were newly diagnosed were described for the first time.

The higher rates of the female sex in the seronegative group are consistent with previous studies.[19,20] The female sex is more prone to produce autoantibodies.[21] Still, multiple genetic and nongenetic risk factors, such as human leukocyte antigen (HLA) genes, particularly shared epitopes, non-HLA genes, and smoking status, contribute to the autoantibody profile.[22] A shorter lag time in Group 4 could result from classification criteria since both RF and anti-CCP are present in the 2010 ACR/EULAR RA criteria.[9] RF and anti-CCP are associated with higher disease activity and erosive radiological changes.[22,23] In addition, CRP, WBC, and NLR titers are associated with disease activity in patients with RA;[24,25] therefore, higher levels of inflammatory markers were an expected result in Group 4. The NLR is an inflammatory marker and is helpful to predict the mortality of cardiovascular events, the prognosis of multiple cancers, and the presence of inflammatory or infectious diseases.[26] There is a correlation between NLR and disease activity in inflammatory rheumatic diseases such as RA, ankylosing spondylitis, and Behçet's disease; NLR is higher in RA patients than healthy controls.[27] We defined the NLR in DMARD-naïve patients with RA for the first time, and it was slightly higher than the healthy Turkish population (2.2 *vs.* 2.0, respectively).[28]

We found that the increasing age was associated with less frequent SJI. This is consistent with medical literature since RA in elderly patients is more prone to develop LJI.[29] Rexhepi et al.[30] reported that shoulder and knee involvement is more frequent in elderly patients with RA than younger patients. An exciting result of our study was the independent predictor role of seronegativity for SJI. It is well known that RF and anti-CCP are independent predictors of bone erosion. Hecht et al.[31] also described the additive effect of dual seropositivity on bone erosion in

patients with RA. Sokolove et al.[32] reported that dual seropositivity is associated with increased systemic inflammation and higher disease activity than other autoantibody profiles. Lingampalli et al.[33] supported previous results and found that dual seropositivity is associated with accelerated progression of RA from the preclinical phase to the clinical phase.

Nonerosive synovitis occurs in 30% of patients with SjS, and joint involvement can mimic RA; RF positivity is present in 44%, and it is associated with arthritis.[34] Additionally, anti-CCP positivity is 33%,[35] which is related to nonerosive arthritis in patients with SjS.[36] RF and anti-CCP are associated with arthritis in patients with systemic lupus erythematosus, which can affect the same articulations as RA.[37,38] Joint manifestation of systemic sclerosis is similar to RA and an early sign of disease; Kamalaksha et al.[39] reported that a combination of RF and anti-CCP positivity is associated with arthritis in patients with systemic sclerosis. On the other hand, ankylosing spondylitis, as a prototype disease of seronegative spondyloarthritis, primarily affects the sacroiliac joint and vertebral column; peripheral arthritis generally occurs in the large joint of the lower extremities, such as the knee or ankle.[40] Thus, we can hypothesize that the importance of the autoantibody profile can vary according to diseases because they have different pathogenesis; additionally, auto-antibodies play a significant role in the pathogenesis of RA.[1]

To date, few studies define the relationship between clinical presentation and disease variables in patients with RA; the first affected joints need to be clearly defined. Van der Helm-van Mil et al.[41] found no initial clinical differences between anti-CCP-positive and -negative patients with RA. Cader et al.[42] supported the previous study and found that knee joint swelling was higher in anti-CCP positivity in early RA patients. Results from the ESPIOR (Etude et Suivi des Polyarthrites Indifférenciées Récentes) cohort suggested that clinical presentation was not closely associated with autoantibody profile. They also reported that hand arthritis was less frequent in seronegative (RF- and anti-CCP-negative) patients with RA. RF and anti-CCP positivity rates were higher in the ESPIOR cohort than our study population (45.8% *vs.* 40.3%, 35.8% *vs.* 35.6%, respectively). The mean ESR and CRP values were also higher in the ESPIOR cohort compared to our study (29.5 *vs.* 20, 22.2 *vs.* 12, respectively).[43] In Korean patients with RA, females had more frequent SJI and less frequent LJI at disease onset.[44] Burgers et al.[45] investigated the first presentation of patients with RA similar to our study; RF or anti-CCP positivity rates were similar between LJI and non-LJI groups. Furthermore, they found that median ESR (40 *vs.* 25, $p<0.001$) and CRP (24 *vs.* 10, $p<0.001$) levels were higher in the LJI group than in the non-LJI group. Conversely, we did not find any relationship between acute phase reactants and joint involvement. Rubbert-Roth et al.[46] showed that median ESR was significantly higher in the LJI group than in the non-LJI group (33.5 *vs.* 18, $p<0.0001$).

The 2010 ACR/EULAR RA classification criteria[9] include acute phase reactants (ESR and CRP), autoantibodies (RF and anti-CCP), and joint involvement (size and count); however, both of these parameters widely vary according to the different geographic regions[15] since the pathogenesis of RA includes multiple genetic and environmental risk factors.[1] Bergstra et al.[15] performed a multicentric study including four countries (Netherlands, India, Mexico, and South Africa) and described the joint distribution of RA at the disease onset. The LJI at the disease presentation varied across countries; for example, knee synovitis was less common in the Netherlands. RF and anti-CCP positivity rates differed from 47.6% to 97.4% and 39.4% to 97.1%, respectively; mean ESR (mm/h) and CRP (mg/L) levels differed from 30±17.7 to 65.7±31.1 and 13.9±26 to 36.7±36.5, respectively. These laboratory parameters of our population were lower than in this study area. The earliest onset of RA was in Indians (with a mean age of 42.7±12.6 years), and the Dutch had the oldest onset (with a mean age of 56±15.5 years). Dutch people have the most similar baseline age and autoantibody profile to the Turkish RA population. This could be due to the geographic proximity between the Netherlands and Türkiye[15] The increased prevalence of seronegative RA within our study population can be attributed primarily to two key factors: the regular practice of conducting hand-wrist radiographs when RA is suspected and the relatively short duration of the disease among the patients. It is worth noting that

seroconversion is a plausible occurrence during the progression of the disease, and there may exist a genetic predisposition among Turkish patients for the development of seronegative RA.[47] We found a high erosivity rate (94%) since the lag time until diagnosis was a mean of 25±36 months. We know that radiological damage is an early manifestation, the fastest radiological progression occurs during the first years, and delayed diagnosis leads to more joint erosions.[48] Presentation with LJI (particularly the knee) has a predictive value for higher radiological erosion rates on small joints during RA,[49] and 27% of our patients presented with LJI. Low hemoglobin concentrations and high scores for ESR are associated with large joint replacement surgery in patients with RA;[50] additionally, 26% of our patients had anemia, and 40.3% had elevated ESR.

This study has some limitations. First, this paper was a retrospective cross-sectional study, which caused a lack of follow-up data, and the study population was small. Second, the first involved joint was described by asking patients since applying to rheumatologists during the first articular symptom is impossible. In addition, we did not examine any inflammatory signs/symptoms on the involved joint in some of the patients who had palindromic onset. Third, baseline Disease Activity Score-28 were absent since nearly half of the patients had achieved nonsteroidal anti-inflammatory drugs before referral to our rheumatology department. Fourth, baseline total Modified Sharp Scores were missing because evaluators lacked sufficient experience. Fifth, we did not detail the involved hand joints, such as the metacarpophalangeal or proximal interphalangeal joints, since some patients could not localize the involved joints. While the total number of cases in our study may appear numerically high, it is essential to note that the average number of patients per month is 25, which equates to slightly over one patient per workday. This figure, we believe, is within an acceptable range for our study group. This is because our clinic serves as the sole tertiary rheumatology department in a city with a population of over 1.5 million people. We meticulously assess all patients who seek our care on the day of their application, and we maintain collaborative working relationships with primary care physicians and specialists in physical therapy and rehabilitation who refer patients to our rheumatology department through a dedicated RA consultation form.

In conclusion, this study was the first to define the first involved joint and associated factors in recent-onset, DMARD-naïve RA patients. The baseline characteristics of the Turkish RA population were also described for the first time. The unique results suggested that age and seronegativity were the independent predictive factors for SJI. One in five RA patients did not present with the classical SJI, and 49.3% had seronegative serology, indicating that the long lag time was a real issue. We hope our result will pay attention to the sensitivity of the RA classification criteria according to the geographic region. Prospective studies with a larger sample size are needed to define the significance of the first involved joints.

Ethics Committee Approval: The study protocol was approved by the Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine Ethics Committee (date: 07.06.2023, no: 04/15- 2023). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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