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Investigation of remission with ultrasound in patients with rheumatoid arthritis according to different clinical remission criteria

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ABSTRACT

Objectives: To investigate remission with ultrasound (US) in patients with Rheumatoid arthritis (RA) according to different clinical remission criteria.

Methods: A total of 105 patients with RA who were in remission for at least 6 months according to disease activity score in the 28 joints using C-reactive protein (DAS28-CRP) were included in the study. US remission rates were analyzed according to different remission criteria [DAS28-CRP, DAS28 using erythrocyte sedimentation rate (DAS28-ESR), clinical disease activity index (CDAI), simplified DAI (SDAI), and the 2011 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Boolean remission criteria]. US remission was determined as power doppler (PD) US score = 0.

Results: Remission rates achieved for each remission criteria were 100%, 82.9%, 55.2%, 58.1% and 42.9% and US remission rates were 57.1%, 57.5%, 53.4%, 55.7%, 57.7% for DAS28 CRP, DAS 28 ESR, CDAI, SDAI, 2011 ACR/EULAR remission criteria, respectively. When the patients compared for the US findings between remission and non-remission patients according to the different clinical remission criteria, no difference was found ($p > 0.05$).

Conclusions: This study shows that clinical remission criterias are not sensitive enough to accurately detect remission and there was no increase in the US remission rates as per the stricter remission criteria. Using US in addition to the clinical criteria would prove to be more useful in evaluating remission.

Keywords: Clinical remission, ultrasonographic remission, rheumatoid arthritis, subclinical synovitis, DAS28 CRP, remission criteria

Rheumatoid arthritis (RA) is a chronic inflammatory disease that can cause bone erosions and joint motion limitation. The treatment of RA aims to suppress inflammation by achieving low disease activity and/or complete remission [1, 2]. Clinical remission is defined as the absence of significant signs and symptoms of inflammatory disease activity and the elimination of any signs of systemic inflammation. The definition of clinical remission in RA is developed by evaluating composite scores of disease activity. These composite scores include the following: disease activity score in the 28 joints using erythrocyte sedimentation rate (DAS28-ESR), the DAS28 using C-reactive protein (DAS28-CRP), clinical disease activity

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index (CDAI), simplified DAI (SDAI), and the 2011 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Boolean remission criteria [3-5]. Reported remission rates depend on the criteria that are used to define remission and may vary in relation with each other [6]. Using the combination of tumor necrosis alpha inhibitor (TNFi) and conventional synthetic disease-modifying drugs (csDMARDs) is predicted to increase clinical remission rates and provide greater control of radiographic progression [7-9]. However, despite achieving the goal of remission, patients who receive only csDMARD and patients who receive both TNFi + csDMARD, experience progressive structural and functional damage. Because although the patients are in clinical remission, subclinical synovitis may persist that can only be detected radiologically. Therefore, the validity of these criteria is controversial. Besides, with stricter remission criteria, higher rates of US remission are expected. In recent years, many attempts have been made to redefine the concept of remission in RA. Studies show that ultrasound (US) is more sensitive than clinical findings in detecting inflammation and can be used to define remission [10-16]. Synovial hypertrophy (SH) and power Doppler (PD) signals are used in the detection of subclinical synovitis using US. Since PD shows synovial vascularity, it reflects active inflammation better [17-19]. The detection of subclinical synovitis in patients in remission is very important for the prognosis of RA and has been emphasized to be the most important predictor of radiographic damage [20-22].

The issues such as which clinical remission criteria are better to reflect true remission, which remission criteria should be used, and whether US findings should be added to the definition of remission are controversial. Therefore, in this study, it was aimed to investigate remission with US according to different clinical remission criteria and to determine which clinical remission criteria is more effective in predicting US remission in RA patients who receive csDMARD alone and combination of TNFi + csDMARD.

METHODS

Study Design and Patient Selection

A total of 105 patients with RA were included in the study. These patients were in remission for at least 6 months, and 55 of these patients received a combination of TNFi + csDMARD and 50 of them received csDMARD alone. Demographic data such as age, gender, smoking habit, and current medication usage were collected from the patients. The study received ethics approval from the local ethics committee of the Uludag University School of Medicine on June, 07 2016 (approval number: 2016-11/27), and written informed consent was obtained from the patients. The study was conducted in Rheumatology outpatient clinic of Uludag University Faculty of Medicine.

Inclusion Criteria

Patients who met the following five criteria were included in the study: 1) diagnosed with RA according to the 1987 revised ACR and/or 2010 ACR/EULAR criteria, 2) >18 years old, 3) in remission according to DAS28-CRP (DAS 28-CRP < 2.6), 4) no swollen joint 5) no disease exacerbation in the last 6 months, 6) achieved stability of treatment in the last 6 months and did not require a change of treatment.

Patients using stable doses of nonsteroidal anti-inflammatory drugs (NSAIDs) and steroids (< 7.5 mg prednisolone or equivalent taken orally every day) were included in the study.

Exclusion Criteria

Patients with RA who were younger than 18 years of age, did not receive treatment, required a change of treatment in the last 6 months, and were administered intra-articular steroid injections into the wrist or other joints during an examination within the last 6 months were not included in the study.

Clinical and Laboratory Evaluation

Clinical and physical assessments were performed. This included the tender joint count (TJC), swollen joint count (SJC), the physicians' [physician global assessment (PhGA)] and patients' [patient global assessment (PtGA)] visual analog scale (VAS) scores (0-10), and Health Assessment Questionnaire (HAQ) scores. All these parameters were evaluated by a rheumatologist. ESR, CRP, rheumatoid factor (RF), and anticyclic citrullinated peptide (anti-CCP) levels were measured; DAS28-ESR, DAS28-CRP, CDAI, SDAI values were calculated for each patient; and the 2011 ACR/EULAR Boolean remission criteria were

evaluated.

Ultrasonographic Evaluation

With respect to the US examination of the joints, SH and PD scores were evaluated according to the definitions of the Outcome Measures in Rheumatology Clinical Trials and using a standard methodology to assess synovial vascularity [23]. US was performed by an experienced rheumatologist (SE).

On the same day, after clinical examination and patient evaluation, seven joints including the 2nd and 3rd metacarpophalangeal (MCP) joint, 2nd and 3rd proximal interphalangeal joint (PIP), wrist (radiocarpal and intercarpal joints), the 2nd and 5th metatarsophalangeal (MTP) joints were evaluated bilaterally using US [24]. That is, a total of 14 joints were evaluated. SH was evaluated using US, and PD was performed with the 6-18 MHz multifrequency linear-probe MyLab60 (ESAOTE, Genova, Italy) ultrasound machine. PD pulse repetition frequency was set to 750 Hz. The Doppler color gain setting was reduced until the artifacts under the bone cortex disappeared.

Each joint was semiquantitatively scored from 0 to 3 for B-mode SH and synovial PD signal. SH scoring was as follows: 0 = no synovial hypertrophy, 1 = mild, 2 = moderate, and 3 = severe; PD scoring was as follows: 0 = normal/minimal vascularity, 1 = mild hyperemia, 2 = moderate hyperemia, and 3 = distinct hyperemia. US scores were expressed as the sum of the scores obtained per joint for all the joints of each patient [23].

The Definition of Remission

Clinical Remission

Remission criteria were determined to be DAS28-CRP < 2.6, DAS28-ESR < 2.6, CDAI < 2.8, SDAI ≤ 3.3, and 2011 ACR/EULAR remission criteria (At any time point, a patient must satisfy all of the following: TJC≤ 1, SJC ≤ 1, CRP ≤ 1 mg/dl and PhGA ≤ 1 (on a 0-10 scale) or Index-based definition at any time point, a patient must have SDAI ≤ 3.3) [5, 25].

Ultrasonographic Remission

There are several different ultrasonographic remission criteria such as strict remission (all SH and PD = 0), a less strict remission (all SH and PD ≤ 1), and remission criteria based solely on PD absence (PD = 0). In the study remission criteria based solely on PD absence (PD = 0) was used as US remission criteria.

Statistical Analysis

The statistical analyses were performed using the IBM SPSS Statistics for Windows, Version 21.0 (Armonk, NY: IBM Corp.) statistical analysis package program. The Kolmogorov–Smirnov test was used to test whether the data were normally distributed. For descriptive variables that did not fit the normal distribution, median (minimum–maximum) values were given. For the comparison of two independent groups, the independent samples t-test was used for the variables that conformed to the normal distribution and the Mann–Whitney U test was used for the variables that did not conform to the normal distribution. The chi-square test was used for qualitative variables that did not fit the normal distribution. A univariable logistic regression was conducted to investigate factors associated with the imaging outcomes. The significance level was set at $p = 0.05$.

RESULTS

Demographic Data and Drugs Used

The demographic data, remission criteria, using drugs, laboratory and US findings of RA patients who receive only csDMARD and both TNFi + csDMARD are shown in Table 1. The median disease duration was 10 years and the remission duration was 12 months. The disease duration in the combination group was found to be significantly higher than that in the csDMARD group ($p = 0.035$). There was no difference between the two groups in terms of the use of methotrexate (MTX) (p = 1.00), leflunomide (LEF) ($p = 0.416$), sulfasalazine (SLZ) ($p = 0.824$), and hydroxychloroquine (HCQ) ($p = 0.846$) (Table 1) With regard to the distribution of TNFi use in the combination group, 23.6% (n = 13) of the patients were using adalimumab, 21.8% (n = 12) were using golimumab, 21.8% (n = 12) were using certolizumab, 20% (n = 11) were using etanercept, and 12.7% (n = 7) were using infliximab.

Remission Rates Achieved for Each Remission Criteria

Remission rates achieved for each remission criteria were 82.9% (n = 87) for DAS-28 ESR, 55.2% (n = 58) for CDAI, 58.1% (n = 61) for SDAI, 42.9% (n

Table 1. Demographic data, remission criteria, drugs, laboratory and ultrasonographic datas of the patients

	All patients (n = 105)	TNFi and csDMARD combination group (n = 55)	csDMARD group (n = 50)	*p* value
Demographic data				
Age (years) †	55 (14-85)	56.00 (23-76)	50.00 (19-85)	0.426
Gender (F), n (%)	83 (79)	45 (81.8)	38 (76)	0.483
Smoking habit, n (%)	47 (44.8)	21 (38.2)	26 (52)	0.173
Disease duration (years) †	10 (1-38)	7.00 (1-13)	2.00 (1-8)	**0.035**
Disease duration (> 5 years), n (%)	81 (77.1)	47 (85.5)	34 (68)	**0.029**
Remission duration (months) †	12.00 (6-60)	8.00 (6-20)	7.50 (6-12)	0.371
Remission duration (> 12 months), n, (%)	47 (44.8)	21 (38.2)	26 (52)	0.173
Remission criteria				
DAS 28-CRP †	1.87 (1.35-2.57)	1.86 (1.46-2.56)	1.88 (1.35-2.57)	0.508
DAS 28-CRP < 2.6, n (%)	105 (100)	55 (100)	50 (100)	1.000
DAS 28-ESR †	2.00 (0.80-.3.5)	2.30 (0.80-3.50)	1.95 (0.80-2.90)	0.104
DAS 28-ESR < 2.6, n (%)	87 (82.9)	40 (72.7)	47 (94)	**0.004**
CDAI †	2.50 (0-7)	2.50 (0-5.50)	2.50 (0-7.00)	0.925
CDAI ≤ 2.8, n (%)	58 (55.2)	31 (56.4)	27 (54)	0.698
SDAI †	3.05 (0-7)	3 (0.30-5.8)	3.15 (0.60-7.30)	0.946
SDAI < 3.3, n (%)	61 (58.1)	34 (61.8)	27 (54)	0.436
ACR/EULAR Remission †	2.30 (0.3-5.3)	2.30 (0.30-4.80)	2.30 (0.30-5.30)	0.475
ACR/EULAR Remission, n (%)	45 (42.9)	27 (49.1)	18 (36)	0.236
TJC, 28 joints†	0 (0-.2)	0 (0-2)	0 (0-2)	0.805
HAQ†	0 (0-0.9)	0 (0-0.9)	0 (0-0.9)	0.861
PtGA VAS (0–10) †	1.5 (0-3)	1.5 (0-3.00)	1.5 (0-3)	0.416
PhGA VAS (0–10) †	1.00 (0-2)	1.00 (0-1.50)	0.50 (0-2)	0.328
Drugs used				
Glucocorticoid usage, n (%)	41 (39)	23 (41.8)	18 (36)	0.556
MTX usage, n (%)	71 (67.6)	37 (67.3)	34 (68)	1.000
LEF usage, n (%)	36 (34.3)	21 (38.2)	15 (30)	0.416
SLZ usage, n (%)	26 (24.8)	13 (23.6)	13 (26)	0.824
HCQ usage, n (%)	45 (42.9)	23 (41.8)	22 (44)	0.846
Laboratory tests				
ESR (mm/h) †	13 (2-526)	14.00 (2-56)	13.00 (2-28)	0.188
CRP (mg/dL) †	0.30 (0.10-1)	0.30 (0.10-1)	0.40 (0.10-0.9)	0.059
RF (IU/ml) †	45 (4-2180)	39.00 (9.50-1280)	45 (4-2180)	0.887
Anti-CCP (IU/ml) †	109.3 (3-1520)	99.00 (3.00-1520)	145.5 (3-1398)	0.526
Ultrasound results				
Total_SH †	4 (0-17)	4 (0-14)	2.50 (0-17)	**0.048**
Total_PD †	0 (0-11)	0 (0-11)	0 (0-8)	0.578
Total_SH_PD †	5 (0-20)	5 (0-19)	4 (0-20)	0.122
SH score = 0, n (%)	28 (26.7)	9 (16.4)	19 (38)	**0.015**
SH score ≥ 2, n (%)	67 (63.8)	41 (74.5)	26 (52)	**0.025**
PD score = 0, n (%)	60 (57.1)	30 (54.5)	30 (60)	0.693
PD score ≥ 1, n, (%)	45 (42.9)	25 (45.5)	20 (40)	0.693
PD score ≥ 2, n (%)	36 (34.3)	20 (36.7)	16 (32)	0.684
SH score = 0, PD score = 0, n (%)	23 (21.9)	8 (14.5)	15 (30)	0.063

Values are presented as median (minimum–maximum) and percentage. Comparison between groups via Mann–Whitney U test and the Pearson's chi-square test with a value of $p < 0.05$ was considered significant. † Median (minimum–maximum). F = female, TNFi = tumor necrosis alpha inhibitör, csDMARD = conventional synthetic disease-modifying antirheumatic drugs, DAS28-CRP = disease activity score in the 28 joints using C-reactive protein, DAS28-ESR = DAS28 using erythrocyte sedimentation rate, CDAI = clinical disease activity index, SDAI = simplified DAI, ACR/EULAR remission = 2011 American College of Rheumatology/European League Against Rheumatism Boolean remission criteria, TJC = tender joint count, HAQ = Health Assessment Questionnaire, PtGA = patient global assessment, PhGA = physician global assessment, VAS = visual analog scale, MTX = methotrexate, LEF = leflunomide, SLZ = sulfasalazine, HCQ = hydroxychloroquine, ESR = erythrocyte sedimentation rate, CRP = C-reactive protein, RF = rheumatoid factor, Anti-CCP = anti-cyclic citrullinated peptide, SH = synovial hypertrophy, PD = power Doppler

= 45) for 2011 ACR/EULAR Boolean remission criteria. The proportion of patients meeting all the remission criteria was 10.5% (n = 11) (Table 1).

The US Remission Rates According to Different Clinical Remission Criteria

US remission rates according to all the clinical remission criteria were 57.1% (n = 60), 57.5% (n = 50), 53.4% (n = 31), 55.7% (n = 34), 57.7% (n = 26) for DAS28 CRP, DAS 28 ESR, CDAI, SDAI, ACR/EULAR remission criteria, respectively (Table 2).

When the remission rates in the combination and csDMARD groups were compared according to different clinical remission criteria, no significant difference was observed between the two groups according to DAS28-CRP, DAS28-ESR, CDAI, SDAI, and 2011 ACR/EULAR Boolean remission criteria ($p = 0.693$, $p = 0.828$, $p = 0.795$, $p = 0.796$, $p = 0.435$, respectively) (Table 2).

Comparison of the Patients With Remission and Non-Remission According to Different Clinical Remission Criteria

The disease duration, remission duration, TJC, ESR, and CRP values of patients in remission and non-remission and the SH and PD scores determined by the US were compared according to all the remission criteria (Table 3). No differences were found between remission and non-remission patients according to the different clinical remission criteria in US findings ($p > 0.05$).

The Relationship between Ultrasonographic Score and Other Findings

The relationship between PD-SH scores and the disease duration, remission duration, ESR, CRP, RF, anti-CCP, TJC, DAS28-CRP, DAS28-ESR, HAQ, CDAI, SDAI, 2011 ACR/EULAR Boolean remission criteria, PhGA, and PtGA were evaluated via logistic regression. There was a positive correlation both between PD and SH score and disease and remission duration. No correlation was found between US scores and the other parameters (Table 4).

DISCUSSION

This study investigated US remission using different definitions of clinical remission criteria. US remission rates according to all clinical remission criteria were between %53.4-%57.7. There was no increase in US remission rates as per the stricter remission criteria. This suggests that current criteria may lack the sensitivity necessary for accurate remission assessment. Using US in addition to the clinical criteria would prove to be more useful in evaluating remission.

In many studies, it has been reported that some of the patients with RA in remission still have subclinical synovitis and the frequency of the synovitis varies significantly between 50% and 95% as per SH and between 15% to 60% as per PD scores [13, 26, 27].

Table 2. The US remission (PD = 0) rates of the patients according to different clinical remission criterias

Clinical remission criteria	All patients n (%)	TNFi + csDMARD combination group n (%)	csDMARD group n (%)	*p* value
DAS28-CRP (< 2.6)	60/105 (57.1)	30/55 (54.5)	30/50 (60)	0.693
DAS28-ESR (< 2.6)	50/87 (57.5)	22/40 (55)	28/47 (59.6)	0.828
CDAI (< 2.8)	31/58 (53.4)	17/31 (54.8)	16/27 (59.3)	0.795
SDAI (≤ 3.3)	34/61 (55.7)	18/34 (52.9)	16/27 (59.3)	0.796
2011 ACR/EULAR remission criteria	26/45 (57.7)	16/27 (59.3)	10/18 (55.7)	0.435

Values are presented as numbers and percentages. TNFi = tumor necrosis alpha inhibitör, csDMARD = conventional synthetic disease-modifying antirheumatic drugs, DAS28-CRP = disease activity score in the 28 joints using C-reactive protein, DAS28-ESR = DAS28 using erythrocyte sedimentation rate, CDAI = clinical disease activity index, SDAI = simplified DAI, 2011 ACR/EULAR remission criteria = 2011 American College of Rheumatology/European League Against Rheumatism Boolean remission criteria

Table 3. Comparison of the patients with remission and non-remission according to different clinical remission criteria

DAS28-ESR remission criteria			
Variables	**Yes (n = 88)**	**No (n = 17)**	***p* value**
Disease duration (years) †	10 (1-38)	13 (1-37)	0.516
Remission duration (months) †	12 (6-60)	11 (6-36)	0.150
TJC †	0 (0-2)	1 (0-2)	0.001
ESR †	11 (2-32)	35 (18-56)	< 0.001
CRP †	0.30 (0.10-0.90)	0.40 (0.10-1)	0.204
Total SH score †	4 (0-17)	2 (0-14)	0.538
Total PD score †	0 (0-11)	0 (0-6)	0.772
Total_SH and PD score †	5(0-20)	3 (0-18)	0.618
SH score = 0 and PD score = 0, n (%)‡	20 (22.7)	3(17.6)	0.637
SH score = 0, n (%)‡	25 (28.4)	3(17.6)	0.358
SH score ≥ 1, n (%)‡	63 (71.6)	14 (82.4)	0.933
PD score = 0, n (%)‡	51 (58)	9 (52.9)	0.702
PD score ≥ 1, n (%)‡	37 (42)	8 (47.1)	0.644
CDAI remission criteria			
Variables	**Yes (n = 58)**	**No (n = 47)**	***p* value**
Disease duration†	9.5 (1-38)	11 (1-37)	0.155
Remission duration†	12(6-40)	12 (6-60)	0.557
TJC†	0 (0-1)	0 (0-2)	0.002
ESR†	13 (2-56)	13 (2-56)	0.454
CRP†	0.30 (0.10-1.00)	0.31 (0.1-0.9)	0.997
Total SH score†	4 (0-17)	4 (0-14)	0.830
Total PD score†	0 (0-11)	0 (0-7)	0.783
Total_SH and PD score†	4 (0-20)	5 (0-18)	0.579
SH score = 0 and PD score = 0, n (%)‡	14 (24.1)	9 (19.1)	0.572
SH score = 0, n (%)‡	16 (27.6)	12 (25.5)	0.813
SH score ≥ 1, n (%)‡	42 (72.4)	35 (74.5)	0.680
PD score = 0, n (%)‡	33 (56.9)	27 (57.4)	0.955
PD score ≥ 1, n (%)‡	25 (43.1)	20 (42.6)	0.962
SDAI remission criteria			
Variables	**Yes (n = 61)**	**No (n = 44)**	***p* value**
Disease duration†	9 (1-38)	11.5 (1-37)	0.107
Remission duration†	12 (6-40)	12.5 (6-60)	0.458
TJC†	0 (0-1)	0 (0-2)	0.001
ESR†	13 (2-56)	14 (2-56)	0.351
CRP†	0.30 (0.10-1.00)	0.40 (0.1-0.9)	0.312
Total SH score†	4 (0-17)	3.5 (0-14)	0.976
Total PD score†	0 (0-11)	0 (0-7)	0.974
Total_SH and PD score†	4 (0-20)	5 (0-18)	0.754
SH score = 0 and PD score = 0, n (%)‡	14 (24.1)	8 (18.2)	0.433
SH score = 0, n (%)‡	17 (27.9)	11 (25)	0.743
SH score ≥ 1, n (%)‡	44 (72.1)	33 (75)	0.704
PD score = 0, n (%)‡	34 (55.7)	26 (59.1)	0.732
PD score ≥ 1, n (%)‡	27 (44.3)	18 (40.9)	0.651
2011 ACR/EULAR remission criteria			
Variable	**Yes (n = 45)**	**No (n = 60)**	***p* value**
Disease duration†	10 (1-38)	11 (1-37)	0.349
Remission duration†	12 (6-40)	12.5 (6-60)	0.423
TJC†	0 (0-1)	0 (0-2)	0.019
ESR†	13 (2-56)	13.5 (2-56)	0.437
CRP†	0.30 (0.10-1.00)	0.40 (0.1-0.9)	0.216
Total SH score†	4 (0-17)	3.5 (0-14)	0.663
Total PD score†	0 (0-11)	0 (0-7)	0.968
Total_SH and PD score†	4 (0-20)	5 (0-18)	0.881
SH score = 0 and PD score = 0, n (%)‡	9 (20)	14 (23.3)	0.683
SH score = 0, n (%)‡	10 (22.2)	18 (30)	0.372
SH score ≥ 1, n (%)‡	35 (77.8)	42 (70)	0.907
PD score = 0, n (%)‡	26 (57.8)	34 (56.7)	0.909
PD score ≥ 1, n (%)‡	19 (42.2)	26 (43.3)	0.812

†Values are presented as median (minimum–maximum). ‡ Values are in numbers and percentages. Comparison between groups via Mann–Whitney U test and the Pearson's chi-square test with a value of $p < 0.05$ was considered significant. DAS28-CRP = disease activity score in the 28 joints using C-reactive protein, DAS28-ESR = DAS28 using erythrocyte sedimentation rate, CDAI = clinical disease activity index, SDAI = simplified DAI, ACR/EULAR remission = 2011 American College of Rheumatology/European League Against Rheumatism Boolean remission criteria, TJC = tender joint count, ESR = erythrocyte sedimentation rate, CRP = C-reactive protein, RF = rheumatoid factor, Anti-CCP = anticyclic citrullinated peptide, SH = synovial hypertrophy, PD = power Doppler

Table 4. The evaluation of the relationship between PD-SH scores and the disease duration, remission duration, different remission criteria, and laboratory values of the patients

All patients (n = 105)				
	PD score OR (CI)	***p* value**	**SH score OR (CI)**	***p* value**
Disease duration	1.068 (1.012-1.127)	**0.016**	1.312 (1.174-1.467)	**< 0.001***
Remission duration	1.086 (1.030-1.145)	**0.002**	1.099 (1.031-1.172)	**0.004***
DAS28-CRP	0.926 (0.296-2.901)	0.895	0.699 (0.217-2.247)	0.547
DAS28-ESR	0.544 (0.273-1.085)	0.084	1.088 (0.548-2.158)	0.809
CDAI	1.052 (0.808-1.369)	0.708	0.999 (0.762-1.310)	0.994
SDAI	1.028 (0.790-1.337)	0.837	0.980 (0.747-1.284)	0.883
2011 ACR/EULAR remission	1.035 (0.739-1.450)	0.840	0.941 (0.665-1.331)	0.731
PhGA VAS (0–10)	1.059 (0.484-2.318)	0.887	1.160 (0.517-2.602)	0.719
PtGA VAS (0–10)	1.028 (0.670-1.557)	0.901	1.007 (0.648-1.564)	0.977
HAQ	1.024 (0.309-3.388)	0.969	1.213 (0.351-4.192)	0.761
TJC	1.259 (0.632-2.510)	0.513	0.871 (0.431-1.761)	0.700
ESR	0.983 (0.946-1.022)	0.387	1.016 (0.980-1.053)	0.395
CRP	0.911 (0.076-1.098)	0.941	0.403 (0.064-2.551)	0.335
RF	1.000 (0.999-1.002)	0.449	1.001 (0.999-1.002)	0.288
Anti-CCP	1.001 (1.000-1.002)	0.291	1.000 (0.999-1.001)	0.883

Logistic regression was used for the table above. OR = odds ratio, CI = confidence interval, *p value is significant, DAS28-CRP = disease activity score in the 28 joints using C-reactive protein, DAS28-ESR = DAS28 using erythrocyte sedimentation rate, CDAI = clinical disease activity index, SDAI = simplified DAS, ACR/EULAR remission = 2011 American College of Rheumatology/European League Against Rheumatism Boolean remission criteria, PhGA = physician global assessment, PtGA = patient global assessment, VAS = visual analog scale, HAQ = Health Assessment Questionnaire, TJC = tender joint count, ESR = erythrocyte sedimentation rate, CRP = C-reactive protein, RF = Rheumatoid factor, anti-CCP = Anti-cyclic citrullinated peptide

Consistent with other studies, ultrasonographic synovitis was found in 52%-74% of patients who were in remission of them as per SH and in 40%-45% of them as per PD in this study. In the literature, US remission rates vary according to different remission criteria but mostly vary between 35-58% [6, 28]. US remission rates in this study were found to be similar to other studies between patients who received only csDMARDs and those who received a combination of csDMARD and TNFi [15, 16]. These results explain why there is a high probability of relapse when the drug is discontinued or its dose is reduced, even if a patient has achieved clinical remission.

Different criteria are used to evaluate remission in patients with RA. DAS28-CRP is a remission criterion that is easy to calculate; thus, it is frequently used in clinical practice. However, since this criterion can be met (< 2.6) in patients with tender/swelling joints or acute phase elevation, it may not accurately reflect the absence of inflammation. DAS28-ESR is similar to DAS28-CRP in reflecting clinical remission. SDAI and ACR/EULAR remission criteria are known as the more stringent criteria. In previous studies, only one clinical remission criterion was used to evaluate remission, and only a few studies have used and compared different remission criteria [16, 27, 29-31]. In these studies, US remission rates were different according to different remission criteria. For instance, Naredo *et al*. found that US remission rates were significantly lower in patients in remission according to DAS28 than that in patients in remission according to SDAI [30]. Peluso *et al*. found that using ACR remission criteria showed fewer US remission than those using the DAS28 remission criteria [31]. On the other

hand, Balsa *et al*. [29] did not find any significant difference between the ACR/EULAR and DAS28 remission criteria. In addition to this, when SDAI was used, US remission was found to be significantly lower compared to that when ACR and DAS28 criteria were used [29]. In the EULAR targeted therapy recommendations updated in 2019, the ACR/EULAR Boolean remission is now preferred over DAS28 remission because it is emphasized that ACR/EULAR remission criteria are more stringent and reflect remission better than other criteria [32]. Both SDAI and ACR/EULAR remission criteria are considered more stringent measures of remission as it allows for the least abnormalities of variables. In our study, although the remission rates of patients who were in remission according to DAS28 CRP were lower with SDAI and ACR/EULAR remission criteria, which are evaluated as stricter criteria, US remission rates did not change under more stringent criteria. In our study, the 2nd and 5th MTP of the foot joints were also evaluated while performing joint US examinations. The only criteria that evaluate the foot joints are the 2011 ACR/EULAR remission criteria. Therefore, it may be thought that other remission criteria may miss the evidence of disease activity and misclassify patients as in remission and US remission will be detected more frequently with the ACR/EULAR remission criteria. However, it was not as expected in our study. One possible reason for this is that, including the foot joints, the patients were in remission. The most likely explanation may be that current clinical remission criteria are largely subjective, do not take into account subclinical inflammation, and neither clinical criterion is superior to the other in demonstrating remission.

Limitations

The most important limitations of this study are that US evaluation was performed by a single physician and the study is a cross-sectional study with a lack of long-term follow-up results. An important factor that would strengthen the study is the fact that US evaluation should be carried out by at least two physicians and the reliability between the physicians should be checked. Another limitation of this study is that the dose and frequency of NSAIDs used by the patients were not recorded. NSAIDs can modify the symptoms and levels of synovitis by masking the clinical symptoms and signs.

Strengths

In previous studies, the presence of US remission was evaluated according to one or two clinical remission criteria. In this study, US remission rates were investigated according to all remission criteria.

CONCLUSION

This study underlines clinical remission criteria does not clearly indicate the presence of remission and none of the remission criteria are superior to each other to evaluate the US remission. The accurate remission in RA would not rely solely on clinical examination but may require imaging to confirm the remission.

Authors' Contribution

Study Conception: HED; Study Design: YP; Supervision: HED, YP; Funding: HED; Materials: BNC; Data Collection and/or Processing: SE, BY; Statistical Analysis and/or Data Interpretation: SE; Literature Review: BY; Manuscript Preparation: SE and Critical Review: BY, YP.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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