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Original Article

Time-integrated Cumulative Parameters Predictive of Radiographic Progression of Rheumatoid Arthritis: Real-world Data From a Prospective Single-center Cohort

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Objective: With many chronic inflammatory diseases, outcomes are determined by assessing both disease activity at presentation and cumulative activity over time. Here, we investigated whether cumulative activity better reflects the radiographic progression (RP) of rheumatoid arthritis (RA) than measurement of activity at a single time point.

Methods: From a prospective cohort of RA patients, most of whom were treated with anti-rheumatic drugs, we selected 117 subjects for whom laboratory, clinical, and radiographic parameters potentially influencing RP were monitored serially for more than 1 year. X-ray images of both hands and both feet were scored using the van der Heijde modified total Sharp score (mTSS). In addition to cross-sectional values at baseline, longitudinal and cumulative values for each parameter were calculated in a time-integrated and averaged manner.

Results: Among the values measured at baseline, mTSS, but not the baseline erythrocyte sedimentation rate (ESR) or C-reactive protein level, was associated with RP. By contrast, multivariate analyses identified cumulative values such as the cumulative ESR, cumulative tender joint count, cumulative swollen joint count (SJC), and cumulative Disease Activity Score 28-ESR as major determinants of RP. In particular, the cumulative SJC showed the best predictive performance for RP.

Conclusion: This study highlights the importance of cumulative indices for predicting progression of RA. Specifically, dynamic and cumulative values of RA activity-related factors, particularly the cumulative SJC, may be the major determinants of RP in the current practice.

Keywords: Rheumatoid arthritis, Prognosis, Biomarkers

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease that affects multiple joints, resulting in structural damage, functional disability, and reduced quality of life [1]. Radiographic progression (RP) is one of the most important indicators of dis-

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ease severity and cumulative disease activity [2]. Disease activity over time is thought to lead to the occurrence of RP; therefore, clinical studies investigating novel medications as potential treatment for RA have focused on whether the candidates prevent RP as well as attenuating disease activity. A variety of biologic agents and small molecule inhibitors targeting disease-related cytokines and intra-cellular signaling pathways have been developed and shown to be effective at slowing RP [3,4]. Promising results from some large-scale trials suggest that new therapeutic modalities prevent RP almost completely [5]. However, randomized clinical trials and experience in real-world clinical settings show that despite good responses, according to composite indices that are representative of RA activity, RP can occur even with proper management [6].

Diverse composite indices, including the Disease Activity Score with 28 joint counts (DAS28), Clinical Disease Activity Index (CDAI), and Simplified Disease Activity Index (SDAI), are used as therapeutic targets for treat-to-target (T2T) strategies for RA [7]. Composite indices for measuring disease activity comprise different combinations of separate clinical and laboratory parameters, including subjective patient-reported outcomes and objective serum markers such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels. Although disease composite indices are used as a standard tool to determine RA activity, recent studies demonstrate that even when these indices suggest that RA patients are in clinical remission, 20%~30% still show RP [8]. Subclinical joint inflammation on musculoskeletal ultrasonography is also observed in more than half of RA patients in clinical remission [9]. Moreover, levels of the acute phase reactant CRP, which is more easily used as a biomarker for RA activity and is a component of DAS28-CRP, can fall after treatment with biologic agents (particularly with interleukin-6 inhibitors), regardless of the patients' symptoms [10]. Taken together, these reports raise some important questions about whether it is still valid to use these indices as a sole therapeutic guideline for daily practice, particularly in the 'post-biologic' era; therefore, alternative strategies that more sensitively represent RP are needed for optimal management of RA patients [11,12].

To make optimal therapeutic plans, it is important to identify subgroups of RA patients with a poor prognosis who progress rapidly and require aggressive treatment from the beginning. High titers of rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), as well as markers of RA activity (e.g., DAS28, ESR, and CRP), at presentation are regarded as the major predictors of RP during the early phase of RA [13]. Post-hoc analyses of several clinical trials, however, demonstrate that cumulative values for these laboratory and clinical parameters measured at different time-points correlate with RP, although no study has made a direct comparison between one-off and cumulative measurements as a predictor of poor outcome [14]. Moreover, many predictors for RP were identified in well-designed clinical trials conducted in the pre-biologic era [15]; however, it is not clear which parameter(s) is the best predictor of RP in the current T2T strategies with various novel biologic agents.

In the present study, we hypothesized that cumulative measurement of RA activity would better reflect RA progression than measurement at a single time point also in the post-biologic era, as was done in the pre-biologic era. To address this, we investigated which parameter(s) predominantly influences RP in daily clinical practice, and tried to collect clinical and laboratory information from a prospective RA cohort. In addition to baseline values, we calculated cumulative values for each parameter in a time-integrated and averaged manner and then determined whether they better represent RP than a single value.

MATERIALS AND METHODS

Study population

All subjects, samples, and related clinical information were obtained from a prospective cohort of RA patients, all of whom had been monitored regularly at Seoul St. Mary's Hospital between January 2015 and December 2020. All patients were diagnosed as RA by rheumatologists, including both early and established RA, and met the 2010 RA classification criteria of the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) [16]. To evaluate the occurrence of RP, subjects with available plain radiographs of both hands and both feet taken at two separate time-points at least 12 months apart were included. Median values of time intervals between two separate x-ray assessments in each subject were about 15 months (Table 1). In addition, only subjects who visited our rheumatology department at least three times during the period between the acquisition of the two X-ray images were included. At each visit, clinical information such as disease activity indices and laboratory values were assessed, and serum was collected. All subjects provided informed consent in accordance with the

Table 1. Baseline demographic information and medication status

Variable	Total (n=117)	RP (+) (n=20)	RP (−) (n=97)	p-value
Age (yr)	57 (49~65)	55 (46~63)	57 (49~66)	0.411
Female	102 (87.2)	17 (85.0)	85 (87.6)	0.720
Body mass index (kg/m^2)	22.8 (20.6~24.9)	22.4 (20.7~24.3)	22.9 (20.6~25.0)	0.728
Disease duration (yr)	6 (1~13)	7 (3~14)	5 (1~13)	0.606
X-ray f/u duration (mo)	15 (13~19)	16 (13~23)	15 (13~19)	0.588
Smoking	1 (0.9)	1 (5.0)	0 (0)	0.171
Medication status				
Glucocorticoid use	88 (75.2)	13 (65.0)	75 (77.3)	0.263
Pd equivalent (mg)	5.0 (2.5~5.0)	5.0 (2.5~7.5)	5.0 (2.5~5.0)	0.378
csDMARDs				
Methotrexate	73 (62.4)	13 (65.0)	60 (61.9)	0.792
Leflunomide	55 (47.0)	11 (55.0)	44 (45.4)	0.432
Hydroxychloroquine	62 (53.0)	12 (60.0)	50 (51.5)	0.490
Sulfasalazine	7 (6.0)	0 (0)	7 (7.2)	0.602
bDMARDs or tsDMARDs	55 (47.0)	11 (55.0)	44 (45.4)	0.432
Tocilizumab	25	6	19	
Abatacept	18	3	15	
Etanercept	4	0	4	
Adalimumab	3	0	3	
Tofacitinib	3	2	1	
Baricitinib	2	0	2	
DAS28 status*				
Remission	49 (41.9)	6 (20.0)	43 (44.3)	
LDA	17 (14.5)	3 (15.0)	13 (14.4)	
MDA	32 (27.4)	6 (30.0)	26 (26.8)	
HDA	19 (16.2)	4 (20.0)	15 (15.5)	
MDA or HDA	51 (43.6)	10 (50.0)	41 (42.3)	0.525
DAS28 change†				
Stable	72 (61.5)	14 (70.0)	58 (59.8)	
Improvement	38 (32.5)	5 (25.0)	33 (34.0)	
Deterioration	7 (6.0)	1 (5.0)	6 (6.2)	
Target achievement‡	96 (82.1)	14 (70.0)	82 (84.5)	0.196

Values are presented as median (interquartile range) or number (%). RP: radiographic progression, f/u: follow up, Pd: prednisolone, csDMARDs: conventional synthetic disease modifying anti-rheumatic drugs, bDMARDs: biologic disease modifying anti-rheumatic drugs, tsDMARDs: targeted synthetic disease modifying anti-rheumatic drugs, DAS28: disease activity score with 28 joint counts, LDA: low disease activity, MDA: moderate disease activity, HDA: high disease activity, ESR: erythrocyte sedimentation rate. *DAS28 status was evaluated at baseline and remission, LDA, MDA, and HDA were defined according to DAS28-ESR. †DAS28 changes defined as 'Stable' indicate no interval change in the DAS28 during the study period. 'Improvement' denotes a change from MDA or HDA to remission or LDA during the study periods. 'Deterioration' denotes a change from remission or LDA to MDA or HDA. ‡Target achievement is defined as achievement of remission or LDA at the last visit.

principles of the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of Seoul St. Mary's Hospital of the Catholic University of Korea (approval number: KC20SISI0467). Finally, of 351 RA patients included in the cohort, 117 met the criteria for inclusion in the present study and the others were excluded because of lack of clinical information

including radiographs or cumulative laboratory data.

Radiographic assessment

X-ray images of both hands and both feet were scored using the total Sharp score (mTSS, scores ranging from 0 to 448), as modified by van der Heijde [17]. Two experienced rheumatologists, both of whom were blinded to all clinical information, assessed the mTSS on all images independently at the same time. Inter-observer agreement was 0.93, estimated as an intra-class correlation coefficient between the two scores for the same image, as assessed by both observers. Interval changes in the mTSS between two images from the same subject (at baseline and follow up) were denoted as ΔmTSS. We used the mean values of ΔmTSS between the two readers as the primary outcome. Occurrence of RP, abbreviated as RP (+), was defined when the mean ΔmTSS from the two readers was ≥2 during a follow-up period of 12 months.

Clinical parameters and cumulative values

All clinical variables potentially related to RP were collected from the cohort database, including RF levels and ACPA titers, medication status, the tender joint counts (TJC) and the swollen joint counts (SJC) based on 28 joints, and the DAS28-ESR. Cumulative values for each clinical parameter were calculated using a time-integrated and averaged approach, as described previously [18]. The area under the curve (AUC) for each time-point was included in each clinical parameter using the 'trapezoidal' rule, as described previously [18]. For example, if a certain parameter was measured as Y1 and Y2 at the time points of T1 and T2, respectively, the cumulative value for T1 and T2 was calculated as (Y1+Y2)×(T2−T1)/2. The unit of time interval was defined as 1 month. Because the follow-up periods for each subject were different (Table 1), all cumulative values were standardized by being adjusted as the averaged values over 12 months.

Enzyme-linked immunosorbent assay (ELISA)

Several soluble factors have been suggested as novel biomarkers representing disease activity based on their immunological roles in RA pathogenesis. We previously demonstrated that soluble CD14 (sCD14) levels are related to disease activity of RA [19]. Another report also showed sCD14 levels are increased in RA and correlate with disease activity [20]. Therefore, we chose serum sCD14 as the potential biomarker predicting radiographic progression of RA in this study. Serum sCD14 concentrations were measured in an ELISA (R&D Systems, Inc., Minneapolis, MN, USA). Serum samples were obtained from each subject at every visit.

Statistical analysis

All statistical analyses were performed using IBM-SPSS Statistics, version 24.0 (IBM Co., Armonk, NY, USA), and all figures were drawn using GraphPad Prism, version 8.0 (GraphPad software, San Diego, CA, USA). Continuous variables were expressed as the median and interquartile range and were analyzed using the Mann–Whitney U-test due to non-normal distribution of data. Categorical variables were analyzed using the chi-square test or Fisher's exact test. Correlations between clinical variables were analyzed using Spearman's rank correlation coefficient test. Uni-variable and multi-variable logistic regression analyses were carried out to identify clinical factors predicting RP. Variables with a p-value<0.1 in uni-variable analyses were included in multi-variable analyses. A p-value<0.05 was considered significant.

RESULTS

Demographic, medications, and RA activity at baseline

Among the 117 subjects who fulfilled the inclusion criteria, 20 had RP, and the other 97 patients showed no evidence of RP [RP (−)]. There was no difference between the RP (+) group and the RP (−) group with respect to the median values for age, body mass index, disease duration, X-ray follow-up duration, and sex distribution (Table 1). The median disease duration of RA patients was about 6 years. Most patients were taking about 5 mg glucocorticoids (an equivalent dose of prednisolone), plus one conventional synthetic disease modifying anti-rheumatic drug (csDMARDs) such as methotrexate, leflunomide, or hydroxychloroquine. About half of the subjects were receiving biologic DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs). Tocilizumab and abatacept were more frequently applied in study subjects than other types of bDMARDs. Nevertheless, overall medication status was similar between the RP (+) and RP (−) groups (Table 1). There was no difference in the proportions of patients with moderate disease activity or high disease activity (HDA) according to DAS28-ESR at baseline. In addition, there was no difference between the two groups with respect to the percentage of patients who achieved the dis-

ease activity target, defined as remission or low disease activity (LDA), after a mean follow-up period of 15 months (Table 1).

Effect of baseline RA activity-associated variables on RP

The median value for the mTSS in the RP (+) group was significantly higher than that of the RP (−) group (p = 0.022), suggesting that RA patients with more severely damaged joints in the hand and foot X-rays are at greater risk of RP during follow-up. However, at baseline, the median values of DAS28-ESR and its constituents (i.e., the TJC, SJC, ESR, and visual analog scale) were not significantly different between the RP (+) and RP (−) groups (Table 2). At the beginning of the study, there was no difference in RF levels or ACPA positivity with a high titer between the two groups. Moreover, the ESR and CRP level, both of which are representative blood biomarkers of RA activity, as well as serum sCD14 concentrations at baseline were not predictive of RP occurrence.

Effects of cumulative RA activity-related variables on RP

We postulated that cumulative values during follow-up would be more useful for predicting the occurrence of RP than a single value measured at each visit. To prove our hypothesis, we calculated cumulative values for each clinical variable potentially associated with RA activity and compared data from the RP (+) and RP (−) groups. Among the disease activity-related variables examined, cumulative DAS28-ESR, TJC, SJC, and serum sCD14 values were significantly higher in the RP (+) group than in the the RP (−) group, but there was no difference in the cumulative RF, ESR, and CRP values (Figure 1A~G). The cumulative SJC was the most notable variable with the lowest p-value, indicating that it is the most predictive factor of RP (Figure 1H). By contrast, the cumulative values for white blood cell count, hemoglobin concentration, platelet count, and serum albumin level, did not predict RP (data not shown).

Next, we carried out multi-variable analysis of the variables at baseline plus the cumulative values with a p-value<0.1. The results identified mTSS at baseline and the cumulative SJC value as significant predictors of RP (Table 3). Moreover, receiver op-

Table 2. Baseline disease activity variables

Variable	Total (n=117)	RP (+) (n=20)	RP (−) (n=97)	p-value
Tender joint count	1 (0~4)	1 (0~4)	1 (0~3)	0.362
Swollen joint count	0 (0~2)	1 (0~4)	0 (0~2)	0.101
Visual analog scale	50 (30~70)	45 (35~68)	50 (30~70)	0.785
DAS28-ESR	2.94 (1.80~4.65)	3.20 (1.93~4.68)	2.90 (1.75~4.65)	0.480
Baseline mTSS	3 (0~18)	8 (1~52)	2 (0~16)	0.022
WBC count ($\times 10^3/mm^3$)	6.48 (5.08~7.64)	6.61 (4.34~8.01)	6.48 (5.45~7.52)	0.534
Hemoglobin (g/dL)	13.0 (12.2~13.7)	13.1 (12.5~14.0)	13.0 (12.1~13.6)	0.467
Platelet count ($\times 10^3/mm^3$)	256 (207~315)	276 (222~334)	254 (206~315)	0.259
Albumin (g/dL)	4.1 (3.9~4.4)	4.1 (3.9~4.4)	4.2 (3.9~4.4)	0.788
RF (IU/mL)	76.7 (25.7~182.0)	48.9 (18.7~461.9)	77.8 (27.1~171.4)	0.775
RF positivity	93 (79.5)	15 (75.0)	78 (80.4)	0.556
RF high positivity*	66 (56.4)	9 (45.0)	57 (58.8)	0.258
ACPA positivity	31/37 (83.8)	5/6 (83.3)	26/31 (83.9)	0.999
ACPA high positivity*	29/37 (78.4)	5/6 (83.3)	24/31 (77.4)	0.999
ESR (mm/h)	14 (3~31)	19 (3~48)	12 (3~31)	0.561
CRP (mg/dL)	0.19 (0.04~1.12)	0.16 (0.04~2.22)	0.21 (0.04~1.07)	0.828
sCD14 (pg/mL)	1,961 (1,725~2,392)	2,071 (1,833~2,300)	1,922 (1,714~2,431)	0.588

Values are presented as median (interquartile range) or number (%). RP: radiographic progression, DAS28: Disease Activity Score 28, ESR: erythrocyte sedimentation rate, mTSS: modified total Sharp score, WBC: white blood cell, RF: rheumatoid factor, ACPA: anti-citrullinated protein antibody, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, sCD14: soluble CD14. *High positivity is defined as >3× the upper limit of normal.

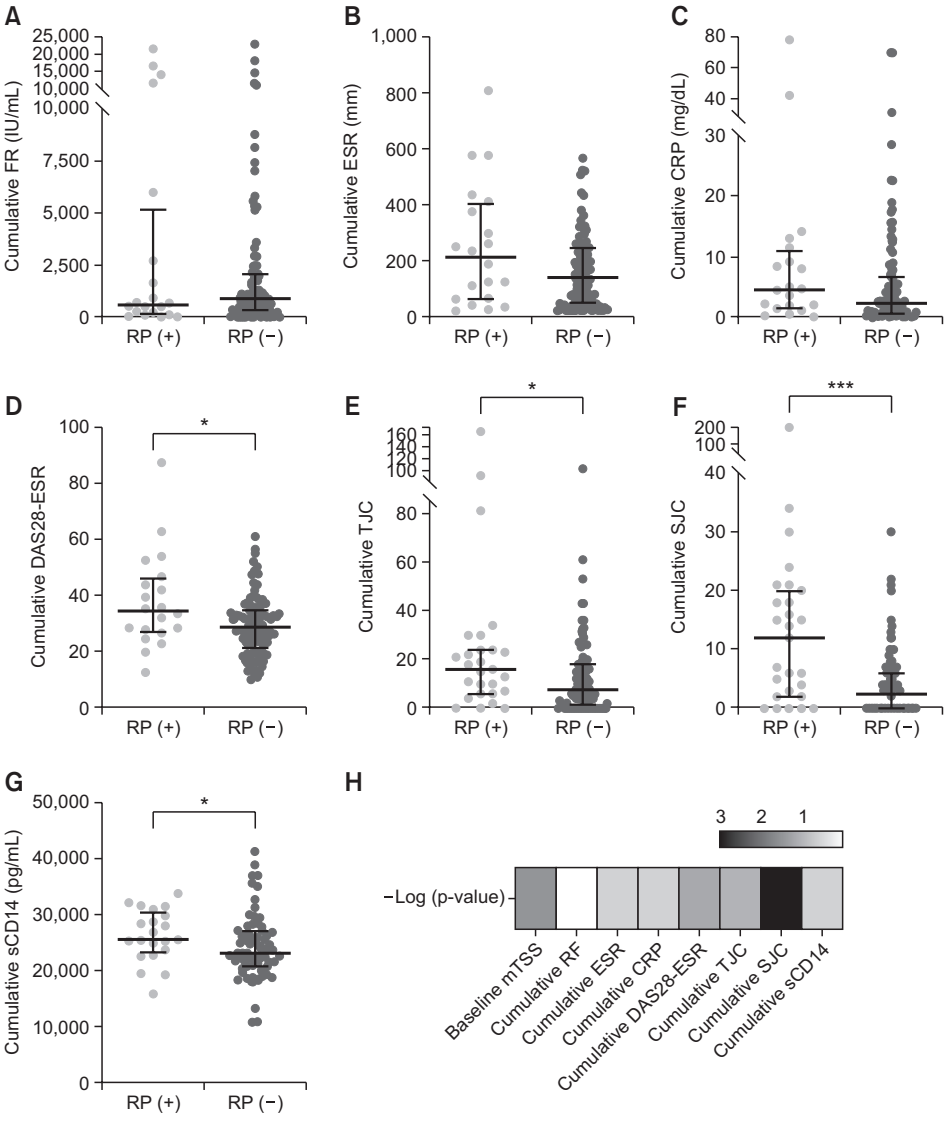


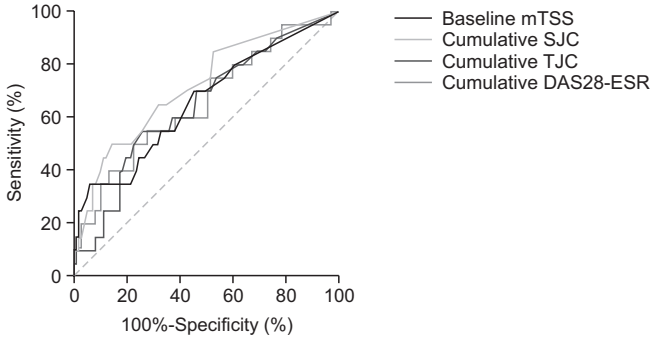
Figure 1. Time-integrated cumulative values of clinical parameters related to rheumatoid arthritis disease activity. (A~G) Cumulative values of RF, ESR, CRP, DAS28-ESR, TJC, SJC, and sCD14. (H) Heatmap showing the p-value represented by −log (p-value). Bars indicate the median and interquartile ranges. All statistical analyses were performed using the Mann–Whitney U-test. RP: radiographic progression, RF rheumatoid factor, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, DAS28: Disease Activity Score 28, TJC: tender joint count, SJC: swollen joint count, sCD14: soluble CD14, mTSS: modified total Sharp score. *p<0.05, ***p<0.001.

Table 3. Baseline and cumulative variables associated with the occurrence of radiographic progression

Variable	Uni-variable (not adjusted)			Model 1* (uni-variable)			Model 2† (multi-variable)		
	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value
Baseline mTSS	1.024	1.007~1.041	0.022	1.036	1.011~1.062	0.004	1.036	1.010~1.063	0.006
Cumulative RF (IU/mL)	1.000	1.000~1.000	0.854	1.000	1.000~1.000	0.102			
Cumulative ESR (mm/h)	1.003	1.000~1.006	0.134	1.004	1.001~1.007	0.013	1.001	0.993~1.008	0.887
Cumulative CRP (mg/dL)	1.021	0.990~1.053	0.134	1.024	0.993~1.057	0.133			
Cumulative TJC	1.020	1.001~1.040	0.037	1.026	1.004~1.048	0.021	0.978	0.936~1.014	0.384
Cumulative SJC	1.090	1.029~1.155	0.001	1.099	1.034~1.167	0.002	1.099	1.019~1.185	0.014
Cumulative DAS28-ESR	1.053	1.013~1.095	0.029	1.060	1.018~1.103	0.005	1.017	0.894~1.156	0.802
Cumulative sCD14 (pg/mL)	1.000	1.000~1.000	0.148	1.000	1.000~1.000	0.245			

CI: confidence interval, mTSS: modified total Sharp score, RF: rheumatoid factor, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, TJC: tender joint count, SJC: swollen joint count, DAS28: disease activity score 28, sCD14: soluble CD14. *Model 1: adjusted for age, sex, and disease duration. †Model 2: clinical variables with p-values < 0.1 in 'Model 1' were included in multi-variable analysis with adjustment for age, sex, and disease duration.

A



B

	AUC	p-value	Sensitivity	Specificity	Cut-off values
Baseline mTSS	0.659	0.025	0.550	0.619	5
Cumulative SJC	0.720	0.002	0.650	0.691	6
Cumulative TJC	0.647	0.040	0.600	0.639	13
Cumulative DAS28-ESR	0.656	0.030	0.600	0.619	31.95

Figure 2. Diagnostic performance of the baseline mTSS, cumulative SJC, cumulative TJC, and cumulative DAS28-ESR for discriminating radiographic progression (RP). (A) Receiver operating characteristic curves of baseline mTSS, cumulative SJC, cumulative TJC, and cumulative DAS28-ESR. (B) Sensitivity, specificity, and cut-off values for clinical parameters predicting occurrence of RP. mTSS: modified total Sharp score, SJC: swollen joint count, TJC: tender joint count, DAS28: Disease Activity Score 28, ESR: erythrocyte sedimentation rate.

erating characteristic curve analysis revealed that the baseline mTSS, cumulative TJC, cumulative SJC, and cumulative DAS28-ESR showed a significant association with RP (Figure 2). Interestingly, the cumulative SJC showed the highest AUC (0.720), with a sensitivity of 0.650 and a specificity of 0.691 (Figure 2), suggesting that it has the best predictive performance for discriminating RP (odds ratio [95% confidence interval]=1.107 [1.031~1.189], p=0.005). The cut-off value at which the cumulative SJC predicted occurrence of RP was 6, indicating that if the total SJC over the following 12 months is >6, then there should be an increase in the mTSS of more than two points.

DISCUSSION

Most randomized clinical trials for RA are designed to limit potential biases. However, the main aim is to evaluate the therapeutic efficacy of target drugs, not to assess clinical relationships between disease-related parameters and RP; therefore, the results can be different from those observed in clinical practices. Here, we investigated which of the clinical and laboratory parameters used in daily clinics, and known to be related to RA disease activity, predict the presence and extent of RP in our prospective cohort. The results show that among all the clinical, laboratory, and radiographic values measured at the start of the study, baseline mTSS was the only parameter predicting the occurrence of RP with statistical significance. In sharp contrast, we found that cumulative values, including the cumulative TJC, cumulative SJC, and cumulative DAS28-ESR, were the major factors to determine RP. In particular, the cumulative SJC showed the best predictive performance.

The RF and ACPA titers are crucial predictors of structural damage specifically in newly diagnosed or early RA patients [21-23]. In the present study, we found no difference in RF and ACPA titers at baseline, and the cumulative RF values between the RP (+) and RP (−) groups, suggesting that RF and ACPA status is less helpful in predicting RP. We presume that these results may be specific to our population, in which the majority of patients had a relatively long disease duration (median 6 years) and had already been treated with anti-rheumatic drugs that may affect RF and ACPA levels. Indeed, previous studies report that RF and ACPA positivity and titers are relevant to early RP during the first 3~5 years of RA [21,22]. Early application of biologic agents that repress the pathogenic activity of autoantibodies could also affect RP in real-world settings as would recent treatment strategies (e.g., T2T strategies) [24,25].

Another important question is which baseline values predict RP. In the current study, we found that baseline mTSS was the only factor that predicted the occurrence of RP. Previous studies report that radiographic damage at the time of diagnosis is a strong predictor of a poor prognosis, which supports our data [26]. Because the mTSS at a certain time-point is the result of accumulated disease activity [27], it is reasonable to assume that patients with high baseline mTSS are at higher risk of more aggressive RP at the next follow-up. It is also possible that damaged joints at the time of study entry are more susceptible to injury and inflammation, and that repetitive use may contribute to further exacerbation of radiographic severity, further increasing the risk of RP.

A single measurement of RA activity (e.g., ESR, CRP, sCD14, or DAS28-ESR) is likely to be less informative for predicting RP in the real-world, particularly in the new era of T2T strategies and biologics. Obviously, RA activity levels at the time of RA diagnosis are a major factor determining disease progression and treatment outcomes; however, several studies demonstrate the occurrence of RP despite low ESR and CRP levels, indicating

that low levels of such parameters do not guarantee lack of progression [28]. Single measurements of DAS28 also exhibit a similar trend [12], which is consistent with our data. Here, we tried to suppress the RA flare as much as possible by applying new or different bDMARDs and tsDMARDs immediately. Therefore, in the clinical settings of our tertiary referral hospital, baseline levels of ESR, CRP, and DAS28 are tightly controlled below the cut-off level for almost all patients throughout the study periods. Most subjects, almost 80% in fact, reached the goal of treatment, defined as remission or LDA; the median values for the baseline ESR, CRP, and DAS28 were less than the upper limit of LDA, even in the RP (+) group (Table 2). In specific situations of 'after reaching T2T', the clinical and laboratory parameters that predict further progression of RA should be determined.

Here, we demonstrated that cumulative values, including the cumulative TJC, cumulative SJC, and cumulative DAS28-ESR, showed a significant association with RP, suggesting that they are a good surveillance marker for RP, even after the achievement of T2T. Although some studies suggest that time-integrated cumulative values for several clinical and laboratory parameters correlate well with RP, most have not made a direct comparison between various clinical parameters [14]. The present study shows that the cumulative SJC correlated best with RP, indicating that it could be the most relevant factor for predicting RP. Unfortunately, due to lack of clinical information in our cohort, it remains unclear whether the location of the swollen joints has an effect on RP. It is intriguing that cumulative blood biomarkers, such as the cumulative ESR and CRP, were not predictive of RP, emphasizing that physical examinations should be conducted regularly to measure the DAS28 and stressing the need for alternative blood biomarkers that better predict patient outcome.

The study has several limitations. First, because all data were collected from a pre-existing cohort not for this study, there is a possibility of selection bias. Specifically, treatment regimens applied in patients of this study were relatively skewed toward non-TNF bDMARDs such as tocilizumab and abatacept. This point can affect the overall results of this study. Second, we could not control all possible confounding factors, although the demographics of the two study groups were similar between the statistical adjustments. For instance, time when csDMARDs or bDMARDs started or previous history of multiple biologic refractoriness can potentially influence cumulative disease activity, consequently determining radiographic progression. However, all such factors could not be controlled by the statistical adjustments in this study. Third, we did not evaluate other composite indices of RA activity, such as the SDAI and CDAI. Last, the number of patients and period of follow-up for RP are insufficient to make a strong conclusion. In this regard, a large-scale prospective study over a longer duration is required.

Notwithstanding these limitations, this study has several strengths. First, this is the first RP study conducted in the 'post-biologic' era primarily comprising RA patients taking bDMARDs and tsDMARDs, or those requiring multiple csDMARDs; this is a good reflection of current treatment paradigms and guidelines. Second, given that patient selection in randomized controlled trials tends to include subjects with HDA, which can limit generalizability, the real-world nature of this study may make the results more generalizable to daily clinical practice, although it does not eliminate concerns about confounding factors. Third, to the best of our knowledge, this is the first study in which almost all parameters potentially influencing RP at presentation and their cumulative values during follow-up were compared simultaneously and analyzed systematically.

CONCLUSION

Clinical practice in most countries is based on current recommendations proposed by the ACR and EULAR [24,25]. We certainly aimed to achieve at least LDA during RA treatment, but we cannot rely on activity-free status determined by the current composite indices (including DAS28) because RP can occur to some extent despite a good treatment response according to these indices. The present study highlights the importance of measuring cumulative indices in addition to physical examination of swollen joints when predicting RA progression. Specifically, dynamic and cumulative values of RA activity-related factors, including cumulative DAS28, ESR, and CRP levels, are the major factors that determine RP in real practice. The cumulative SJC showed the best predictive performance for RP. A single measurement of clinical indices at a specific time-point might be less informative for predicting RA progression, particularly in patients being treated with anti-rheumatic drugs, including biologics.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Y.P. and W.U.K. conceived and planned the study. Y.P., J.W.K., J.H.K., and W.U.K. recruited the subjects, and collected clinical information and blood samples. Y.P. and M.L.L. conducted the experiments using the blood samples. Y.P., Y.J.P., and W.U.K. analyzed the data. Y.P. and W.U.K. drafted and revised the manuscript. All authors provided critical feedback and helped with research, analyses, and manuscript writing.

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REFERENCES

1. Smolen JS, Aletaha D, Barton A, Burmester GR, Emery P, Firestein GS, et al. Rheumatoid arthritis. Nat Rev Dis Primers 2018;4:18001.
2. van der Heijde D. Radiographic progression in rheumatoid arthritis: does it reflect outcome? Does it reflect treatment? Ann Rheum Dis 2001;60 Suppl 3:iii47-50.
3. Aletaha D, Smolen JS. Diagnosis and management of rheumatoid arthritis: a review. JAMA 2018;320:1360-72.
4. Oh YJ, Park B, Moon KW. Effect of drug adherence on treatment outcome in rheumatoid arthritis. J Rheum Dis 2019;26:264-72.
5. Murray E, Ellis A, Butylkova Y, Skup M, Kalabic J, Garg V. Systematic review and network meta-analysis: effect of biologics on radiographic progression in rheumatoid arthritis. J Comp Eff Res 2018;7:959-74.
6. Park YJ, Gherghe AM, van der Heijde D. Radiographic progression in clinical trials in rheumatoid arthritis: a systemic literature review of trials performed by industry. RMD Open 2020;6:e001277.
7. Anderson J, Caplan L, Yazdany J, Robbins ML, Neogi T, Michaud K, et al. Rheumatoid arthritis disease activity measures: American College of Rheumatology recommendations for use in clinical practice. Arthritis Care Res (Hoboken) 2012;64:640-7.
8. Lillegraven S, Prince FH, Shadick NA, Bykerk VP, Lu B, Frits ML, et al. Remission and radiographic outcome in rheumatoid arthritis: application of the 2011 ACR/EULAR remission criteria in an observational cohort. Ann Rheum Dis 2012;71:681-6.
9. Brown AK, Conaghan PG, Karim Z, Quinn MA, Ikeda K, Peterfy CG, et al. An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. Arthritis Rheum 2008;58:2958-67.
10. Schiff MH, Kremer JM, Jahreis A, Vernon E, Isaacs JD, van Vollenhoven RF. Integrated safety in tocilizumab clinical trials. Arthritis Res Ther 2011;13:R141.
11. Landewé R, van der Heijde D, Klareskog L, van Vollenhoven R, Fatenejad S. Disconnect between inflammation and joint destruction after treatment with etanercept plus methotrexate: results from the trial of etanercept and methotrexate with radiographic and patient outcomes. Arthritis Rheum 2006;54:3119-25.
12. Ten Klooster PM, Versteeg LGA, Oude Voshaar MAH, de la Torre I, De Leonardis F, Fakhouri W, et al. Radiographic progression can still occur in individual patients with low or moderate disease activity in the current treat-to-target paradigm: real-world data from the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry. Arthritis Res Ther 2019;21:237.
13. Forslind K, Ahlmén M, Eberhardt K, Hafström I, Svensson B. Prediction of radiological outcome in early rheumatoid arthritis in clinical practice: role of antibodies to citrullinated peptides (anti-CCP). Ann Rheum Dis 2004;63:1090-5.
14. Navarro-Compán V, Gherghe AM, Smolen JS, Aletaha D, Landewé R, van der Heijde D. Relationship between disease activity indices and their individual components and radiographic progression in RA: a systematic literature review. Rheumatology (Oxford) 2015;54:994-1007.
15. Landewé RB, Boers M, Verhoeven AC, Westhovens R, van de Laar MA, Markusse HM, et al. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. Arthritis Rheum 2002;46:347-56.
16. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569-81.
17. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol 2000;27:261-3.
18. Matthews JN, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. BMJ 1990;300:230-5.
19. Park YJ, Yoo SA, Hwang D, Cho CS, Kim WU. Identification of novel urinary biomarkers for assessing disease activity and prognosis of rheumatoid arthritis. Exp Mol Med 2016;48:e211.
20. Mikuls TR, LeVan TD, Sayles H, Yu F, Caplan L, Cannon GW, et al.

Soluble CD14 and CD14 polymorphisms in rheumatoid arthritis. J Rheumatol 2011;38:2509-16.
21. Listing J, Rau R, Müller B, Alten R, Gromnica-Ihle E, Hagemann D, et al. HLA-DRB1 genes, rheumatoid factor, and elevated C-reactive protein: independent risk factors of radiographic progression in early rheumatoid arthritis. Berlin Collaborating Rheumatological Study Group. J Rheumatol 2000;27:2100-9.
22. Nishimura K, Sugiyama D, Kogata Y, Tsuji G, Nakazawa T, Kawano S, et al. Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. Ann Intern Med 2007;146:797-808.
23. Kim H, Sung YK. Epidemiology of rheumatoid arthritis in Korea. J Rheum Dis 2021;28:60-7.
24. Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol 2016;68:1-26.
25. Smolen JS, Landewé RBM, Bijlsma JWJ, Burmester GR, Dougados M, Kerschbaumer A, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis 2020;79:685-99.
26. Gossec L, Dougados M, Goupille P, Cantagrel A, Sibilia J, Meyer O, et al. Prognostic factors for remission in early rheumatoid arthritis: a multiparameter prospective study. Ann Rheum Dis 2004;63:675-80.
27. Welsing PM, Landewé RB, van Riel PL, Boers M, van Gestel AM, van der Linden S, et al. The relationship between disease activity and radiologic progression in patients with rheumatoid arthritis: a longitudinal analysis. Arthritis Rheum 2004;50:2082-93.
28. Wick MC, Lindblad S, Klareskog L, Van Vollenhoven RF. Relationship between inflammation and joint destruction in early rheumatoid arthritis: a mathematical description. Ann Rheum Dis 2004;63:848-52.