Original Article

Comparison of the Disease Activity Score-28 Based on the Erythrocyte Sedimentation Rate and C-reactive Protein in Rheumatoid Arthritis

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Objective. Assessing the disease activity is a key part of clinical decision-making in rheumatology. In particular, a high disease activity, which is represented by a disease activity score-28 (DAS28) score > 5.1, is used as a cutoff value for the use of biologics in many countries, including Korea. This study compared the DAS28-erythrocyte sedimentation rate (ESR) and DAS28-C-reactive protein (CRP) to determine if these indices can be used interchangeably in patients with high disease activity. **Methods.** This cross-sectional study enrolled 1,117 patients with rheumatoid arthritis and examined the initial registration data from the Korean Biologics Registry. **Results.** In general, DAS28-CRP showed an excellent correlation with DAS28-ESR ($r^2 = 0.889$, p < 0.001). On the other hand, DAS28-CRP tended to underestimate the disease activity in those with moderate-to-high disease activity. The best agreement between DAS28-ESR and DAS28-CRP for defining a high disease activity was achieved using a cutoff value of 4.5 for the latter (kappa, 0.68; sensitivity, 85.9%; specificity, 88.1%). **Conclusion.** DAS28-CRP correlates well with DAS28-ESR; however, the cutoff value of the former needs to be reduced to 4.5 if these two indices are to be used interchangeably to define a high disease activity. **(J Rheum Dis 2017;24:287-292)**

Key Words. C-reactive protein, Rheumatiod arthritis

INTRODUCTION

Assessing disease activity is a key part of clinical decision-making in rheumatology. Both the 2015 American College of Rheumatology (ACR) and 2013 European League Against Rheumatism (EULAR) guidelines for the treatment of rheumatoid arthritis (RA) recommend that the initial decision about treatment is based on disease activity [1,2]. Thereafter, a 'treat to target' approach is adopted, which involves repeated assessment of treatment efficacy and adaptation/adjustment where necessary [3].

Several composite indices are used for dynamic assessment of RA disease activity. While the simple disease activity index (SDAI) is commonly used to define remission as a treatment goal [4], a disease activity score-28 (DAS28) > 3.2 is commonly used as an inclusion crite-

rion for clinical trials [5,6]. Also, a DAS28 > 5.1 (i.e., high disease activity) is used as the cutoff for biologic treatment in many countries, including Korea.

The DAS28 was originally designed as a composite index based on the number of swollen and/or tender joints among 28 designated joints and the erythrocyte sedimentation rate (ESR) [7]. However, because C-reactive protein (CRP) has now replaced the ESR as the main marker of inflammation [8], the DAS28-CRP was developed as a measure of RA disease activity. Although the formula for calculating DAS28-CRP values was designed to produce results similar to those provided by the DAS28-ESR, changes in ESR and CRP levels represent different underlying pathophysiologies; therefore, it is unclear whether the DAS28-ESR and DAS28-CRP can be used interchangeably to assess disease activity in RA with the same cutoffs [9-12].

Therefore, the aim of this study was to compare the DAS28-ESR and DAS28-CRP to see whether they can be used interchangeably to identify patients with high disease activity.

MATERIALS AND METHODS

This cross-sectional study enrolled 1,117 patients with RA and examined initial registration data from the Korean Biologics Registry (KOBIO). All patients who start biologic therapy, switch to another biologic agent, and restart biologic therapy after discontinuation can be registered in the KOBIO. Patients who start early biologic therapy without reimbursement, at their request or to treat extra-articular manifestations, can also be registered. The KOBIO protocol was approved by the Institutional Review Boards and ethics committees of the Chungbuk National University Hospital and relevant participating hospitals (no. CBNUH 2014-12-002).

Data collection

Demographic data (age, gender, disease duration, body mass index, and smoking status) were obtained from the KOBIO database. Also, comorbidities, medication usage, serum levels of rheumatoid factor and anti-cyclic citrullinated peptide antibodies, and markers of disease activity (patient's global assessment [PtGA], physician's global assessment [PhGA], the 28 tender joint count [TJC], the 28 swollen joint count [SJC], and ESR and CRP levels) were collected. PtGA was assessed using the following question: 'Considering all the ways your arthritis affects you, how do you feel your arthritis is today?' Patients responded using a 0~10 cm visual analogue scale (VAS), with 'not active at all' and 'extremely active' as anchors. PhGA was rated by a physician on a 0~10 cm VAS [13].

The DAS28-ESR was calculated as $(0.56*\sqrt{28TJC}+0.28*\sqrt{28SJC}+0.70*\ln(ESR))*1.08+0.16$. The DAS28-CRP was calculated as $(0.56*\sqrt{28TJC}+0.28*\sqrt{28SJC}+0.36*\ln(CRP+1))*1.10+1.15$. The SDAI was calculated as TJC+SJC+PtGA+PhGA+CRP. The clinical disease activity index was calculated as TJC+SJC+PtGA+PhGA [14].

Statistical analysis

Values were expressed as mean (±standard deviation, SD) or as a percentage (%), as appropriate. To examine the relationship between DAS28-CRP and DAS28-ESR values, scatter plots with linear regression lines were constructed and Pearson's correlation coefficient was calculated.

Receiver operating characteristic (ROC) curves were constructed to assess the cutoff points for DAS28-CRP that corresponded to DAS28-ESR scores of 5.1. The cutoff point calculation was based on the best trade-off between sensitivity and specificity as follows: (sensitivity+specificity)/2. To check agreement between the two measures of disease activity, weighted kappa statistics for criteria agreement and the Bland and Altman method were used.

The degree of agreement (κ) was defined as follows: <0, no agreement; 0~0.20, slight agreement; 0.21~0.40, fair agreement; 0.41~0.60, moderate agreement; 0.61~0.80, substantial agreement; and 0.81~1.00, almost perfect agreement [15].

RESULTS

High disease activity as defined by the DAS28-ESR and DAS28-CRP

Data from the 1,117 patients are summarized in Table 1. The mean DAS28-ESR was 5.7±1.1, and the mean DAS28-CRP was 5.0±1.1 (p<0.001, Figure 1A). Defining disease activity using the DAS28-ESR revealed the fol-

Table 1. Demographics and disease characteristics of the 1,117 patients with rheumatoid arthritis

Variable	Patient (n = 1,117)
Female	939 (84.1)
Body mass index (kg/m^2)	22.4 ± 3.3
Age (yr)	57.2 ± 13.1
Smoking status (current smokers)	66 (5.9)
Smoking status (ever smokers)	162 (14.5)
Disease duration (yr)	8.2 ± 7.6
RF positivity (n = 1,084)	930 (85.8)
Anti-CCP antibody positivity (n = 940)	808 (86.0)
Glucocorticoids (currently taking)	972 (87.0)
MTX (ever treated)	1,062 (95.1)
Any biological therapy (ever treated)	317 (28.4)
Hypertension	289 (25.9)
Ischemic heart disease	16 (1.4)
Restrictive/interstitial lung disease	29 (2.6)
Diabetes mellitus	114 (10.2)
Obesity	14 (1.3)
Renal failure	8 (0.7)
Malignancy	11 (1.0)

Values are presented as number (%) or mean±standard deviation. RF: rheumatoid factor, CCP: cyclic citrullinated peptide, MTX: methotrexate.
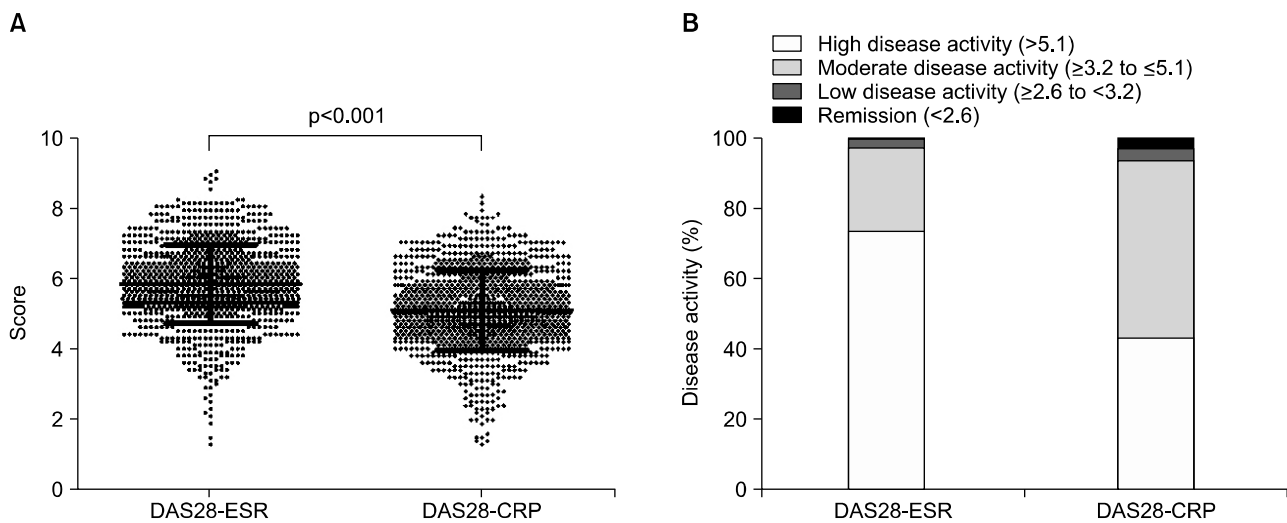
Figure 1. (A) Scatter plot showing the DAS28-ESR and DAS28-CRP scores in this population. Each dot represents the score for a single patient. Bars represent the mean ± standard deviation, which is 5.7 ± 1.1 for DAS28-ESR and 5.0 ± 1.1 for DAS28-CRP. (B) Distribution of disease activity as defined by the DAS28-ESR and DAS28-CRP. DAS28-ESR: 73.8% of patients had high disease activity, 24.4% had moderate disease activity, 1.5% had low disease activity, and 0.8% were in remission. DAS28-CRP: 43.0% of patients had high disease activity, 51.1% had moderate disease activity, 2.9% had low disease activity, and 3.0% were in remission. DAS: disease activity score, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein.

lowing: 73.8% of patients had high disease activity (defined as >5.1), 24.4% had moderate disease activity (≥3.2 to ≤5.1), 1.5% had low disease activity (≥2.6 to ≤3.2), and 0.8% were in remission (<2.6). However, the DAS28-CRP revealed the following: 43.0% of patients had high disease activity, 51.1% had moderate disease activity, 2.9% had low disease activity, and 3.0% were in remission (Figure 1B).

Among 317 patients (28.4%) who had ever received biologic therapy, six patients (0.5%) switched from tocilizumab due to inefficacy (n=4) and because the clinical trial ended (n=2). Their median (range) DAS28-ESR and DAS28-CRP were 6.3 (5.5～7.4) and 5.8 (5.3～6.8), respectively, with a CRP concentration of 4.81 mg/dL (1.8 ～11.94 mg/dL) and an ESR of 66 mm/hr (28～120 mm/hr).

Relationship between DAS28-ESR and DAS28-CRP values

The correlation coefficient (r) for DAS28-ESR versus DAS28-CRP was 0.943, indicating that the DAS28-ESR and DAS28-CRP showed a strong linear correlation (r^2=0.889, p<0.001; Figure 2A). The Bland-Altman plot showed that the mean DAS28-ESR minus DAS28-CRP was 0.73, suggesting that the DAS28-CRP underestimates the overall disease activity in those with moderate-to-high disease activity (Figure 2B).

The current cutoff for high disease activity according to the DAS28-CRP is >5.1. This value showed a sensitivity of 57.3% (95% confidence interval [CI], 53.8～60.7) and a specificity of 98.3% (95% CI, 96.1～99.4) when DAS28-ESR high disease activity (>5.1) was used as the gold standard. The agreement between the DAS28-ESR and DAS28-CRP with respect to high disease activity was fair (κ , 0.40; 95% CI, 0.36～0.45).

The ROC values for DAS28-CRP that corresponded to high disease activity according to the DAS28-ESR revealed that the area under the ROC curve was 0.936. The best trade-off DAS28-CRP value that corresponded to a DAS28-ESR indicating high disease activity was 4.5. The adjusted cutoff showed a sensitivity of 85.9% (95% CI, 83.3～88.2) and a specificity of 88.1% (95% CI, 83.8～91.5) when DAS28-ESR high disease activity (>5.1) was used as the gold standard. The agreement with DAS28-ESR was substantial (κ , 0.68; 95% CI, 0.63～0.73; Table 2).

DISCUSSION

Although the DAS28-CRP and DAS28-ESR correlated well with other activity indices, they showed poor agreement with each other when used to define high disease activity. In this cohort, 78% of patients had high disease activity as defined by DAS28-ESR >5.1. However, the DAS28-CRP >5.1 defined only 43.0% with high disease
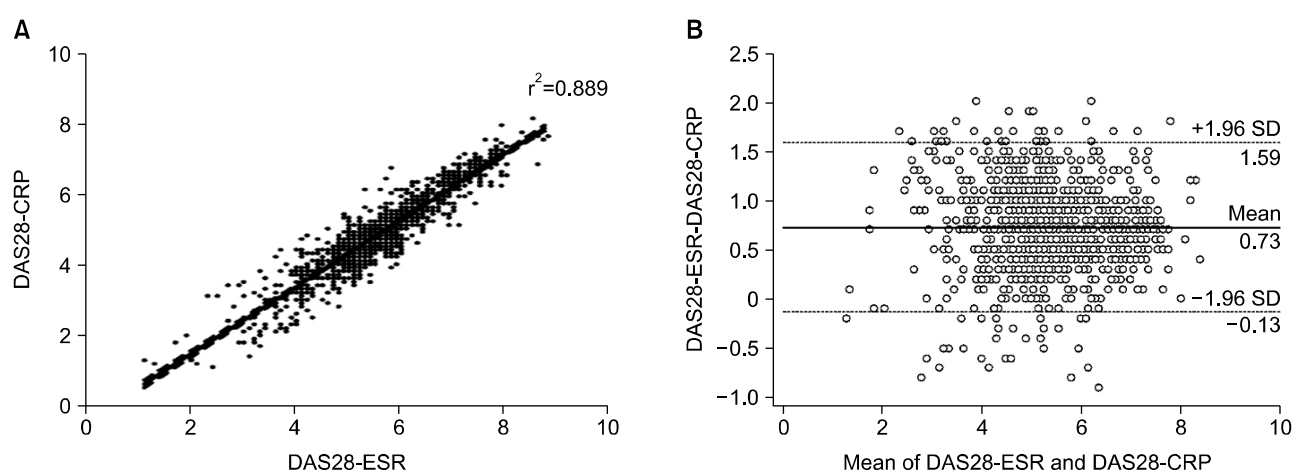
Figure 2. (A) Scatter plot showing DAS28-ESR (x axis) versus DAS28-CRP (y axis) values along with a regression line. The slope and intercept of the regression line were 0.9427 and −0.4004, respectively. Each point represents a single patient, and the scatter lines indicate the 95% confidence interval. (B) Bland-Altman plot of DAS28-ESR and DAS28-CRP. The difference between DAS28-CRP and DAS28-ESR scores (y axis) versus the mean value for DAS28-CRP and DAS28-ESR (x axis) is shown. The mean difference is represented by the central line, and the upper and lower dashed lines represent ±1.96 standard deviation (SD) from the mean. The mean DAS28-ESR minus DAS28-CRP was 0.73, suggesting that the DAS28-CRP underestimates the overall disease activity in those with moderate-to-high disease activity. DAS: disease activity score, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein.

Table 2. Comparison of DAS28-ESR and DAS28-CRP: sensitivity, specificity, and kappa coefficient values according to the cutoffs used to define high disease activity

Criterion	DAS28-ESR cutoff	DAS28-CRP cutoff	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Agreement, kappa (95% CI)
High disease activity	5.1	5.1	57.3 (53.8∼60.7)	98.3 (96.1∼99.4)	0.40 (0.36∼0.45)
	5.1	4.5	85.9 (83.3∼88.2)	88.1 (83.8∼91.5)	0.68 (0.63∼0.73)

DAS: disease activity score, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, CI: confidence interval.

activity, meaning that in 30.8% of cases the DAS28-ESR and DAS28-CRP did not agree.

The relationship between DAS28-ESR and DAS28-CRP has attracted interest in Korea. To the best of our knowledge, Won et al. [16] first commented on the discrepancy between DAS28 and DAS28-CRP in a report about new reimbursement criteria for biologic therapy based on DAS28. When new criteria for biologic initiation, specifically 'DAS28 of more than 5.1 or between 3.2 and 5.1 with radiographic changes', was applied to 299 RA patients who satisfied previous reimbursement criteria for biologic initiation, 93% and 81.6% of these patients satisfied the criteria based on DAS28-ESR and DAS28-CRP, respectively. With regard to this discrepancy, Won et al. [16] suggested that the ESR can be overestimated in females and that it would be beneficial to use DAS28-ESR for aggressive treatment of diseases that affect females more frequently than males, such as RA.

In 2015, Son et al. [17] compared DAS28-ESR and

DAS28-CRP in 540 Korean RA patients due to the previously noted discrepancy between DAS28 and DAS28-CRP. Disease activity varied in their cohort, and the mean DAS28-ESR was 3.65±1.37 and the mean DAS28-CRP was 3.44±1.15. They determined the percentages of patients categorized as having high, moderate, or low disease activity or being in remission based on DAS28-ESR or DAS28-CRP. Although Son et al. [17] did not investigate cutoff adjustment, they demonstrated that 14.8% and 8.0% of patients were classified as having high disease activity based on DAS28-ESR and DAS28-CRP, respectively. In 2016, Song and Lee [18] published a meta-analysis of 11 previous studies concerning DAS28-ESR and DAS28-CRP, and concluded that DAS28-CRP underestimates disease activity and overestimates the EULAR response.

The tendency of ESR elevation with aging was also observed in this study; however, neither gender nor obesity affected the ESR in our cohort (data now shown). We do

not wish to disparage the value of DAS28-ESR because a previous longitudinal study validated DAS28-ESR cutoffs for clinical use [7] and these reflect its overestimation in elderly female patients. DAS28-ESR is a clinically useful tool to assess RA disease activity.

In contrast with DAS28-ESR, DAS28-CRP does not tend to be overestimated in specific groups, resulting in underestimation of disease activity if the same cutoff is used for both DAS28-CRP and DAS28-ESR. As a result, some patients may not receive the aggressive treatment they require. The ESR markedly increases as RA activity increases, meaning its overestimation according to sex and age will become less of a problem. Therefore, it would be better to adjust the cutoff for disease activity rather than modify the formula used to calculate DAS28-CRP. With the re-adjusted optimal cutoff, we expect DAS28-CRP to better reflect disease activity, irrespective of age and sex.

A recent report on this subject by Fleischmann et al. [19] used baseline data from two randomized clinical trials that enrolled patients with early RA who were naïve to methotrexate and biological therapy in Asia, Australia, Europe, and Latin America. Castrejón et al. [10] conducted a similar study in a Spanish early arthritis cohort and recommended that the DAS28-CRP cutoff for high disease activity should be reduced to 4.9. However, only 57% of their cohort satisfied the ACR classification criteria for RA.

Fleischmann et al. [19] compared DAS28-ESR and DAS28-CRP in 834 moderate-to-severe early RA patients and concluded that DAS28-CRP underestimates disease activity and suggested a new cutoff of 4.6, similar to this study. By contrast, an earlier report by Inoue et al. [9] suggested a lower cutoff of 4.1. These differences serve as an important reminder of the racial and ethnic disparities in RA activity measures [20]. We present the optimal cutoff for Korean patients. The results of the present study agree with those of Fleischmann et al.[19], who used a global cohort.

This study has several limitations. First, the results were derived from Korean patients only and so are not generalizable. Although this study is in agreement with that by Fleischman et al.[19], we cannot apply our results to patients in other Asian countries, such as Japan. Second, this is a multicenter study, meaning that there are differences in the methods used to measure CRP levels and differences in the lowest detection range of CRP by each center. However, most patients had CRP levels above the lowest detection range; therefore, we do not believe that this would lead to a significant error. Third, when we applied the adjusted cutoff for DAS28-CRP high disease activity, the agreement with DAS28-ESR high disease activity improved from fair to substantial. However, the interpretation of kappa values according to the Landis and Koch guidelines is not universally accepted; therefore, we used exact kappa values rather than ranges.

Despite these limitations, this is the largest Korean study concerning the discrepancy between DAS28-ESR and DAS28-CRP. Specifically, it analyzed more than 1,000 RA patients using a national multicenter cohort. More than 90% of patients had moderate-to-high disease activity, and thus this cohort was optimal to recalculate the cutoff between high and moderate disease activity. In contrast with the studies by Fleischman et al. [19] and Castrejón et al. [10], this report provides real-world data from patients who have suffered from RA for various durations (mean±SD, 8.2±7.6 years). Like most patients we encounter in the clinic, 95% of patients had received methotrexate and 28.4% of patients had ever been treated with biologic therapy.

CONCLUSION

The DAS28-CRP is a useful index that shows a close correlation with the DAS28-ESR; however, the two are not equivalent because the DAS28-CRP usually classifies fewer patients as having high disease activity. Therefore, to make the two scores more equivalent and thus allow them to be used interchangeably, the cutoff DAS28-CRP value for high disease activity should be lowered to 4.5.

CONFLICT OF INTEREST

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

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