

# Comparison of Disease Activity Score 28 Using C-reactive Protein and Disease Activity Score 28 Using Erythrocyte Sedimentation Rate in Assessing Activity and Treatment Response in Rheumatoid Arthritis: A Meta-analysis

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**Objective.** We compared the Disease Activity Score 28 (DAS28) using C-reactive protein (DAS28-CRP) with DAS28 using erythrocyte sedimentation rate (DAS28-ESR) in assessing rheumatoid arthritis (RA) activity and determining European League Against Rheumatism (EULAR) response criteria. **Methods.** We searched the PubMed, EMBASE, and Cochrane databases and performed a meta-analysis to examine comparisons between DAS28-CRP and DAS28-ESR by RA activity and EULAR response criteria. **Results.** A total of ten studies were included in this meta-analysis. Significantly more patients were classified as having remission or low disease activity when using DAS28-CRP than when using DAS28-ESR (odds ratio [OR] = 1.869, 95% confidence interval [CI] = 1.180 to 2.959,  $p = 0.008$ ; OR = 1.411, 95% CI = 1.256 to 1.586,  $p = 7.0 \times 10^{-8}$ ), whereas fewer patients were classified as having high disease activity when using DAS28-CRP than when using DAS28-ESR (OR = 0.534, 95% CI = 0.388 to 0.734,  $p = 1.1 \times 10^{-4}$ ). More patients were classified as having good response with criteria were based on DAS28-CRP than with DAS28-ESR (OR = 1.390, 95% CI = 1.183 to 1.632,  $p = 6.10 \times 10^{-5}$ ). **Conclusion.** Our meta-analysis demonstrates that DAS28-CRP underestimates disease activity and overestimates response by the EULAR response criteria compared to DAS28-ESR. (*J Rheum Dis* 2016;23:241-249)

**Key Words.** DAS28-CRP, DAS28-ESR, Rheumatoid arthritis

## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease that predominantly affects the synovial joints, causing significant morbidity and shortened life expectancy [1]. The Disease Activity Score based on 28 joints (DAS28) has been widely used and validated in clinical practice and trials to monitor RA disease activity and determine treatment response using the European League Against Rheumatism (EULAR) response criteria [2]. DAS28 is calculated from 4 components: number of tender joints, number of swollen joints, visual analogue scale score of the patient's global health, and erythrocyte sedimentation rate (ESR) [3]. Since ESR is used as an in-

flammation marker, this version is referred to as DAS28-ESR. ESR is affected by age, sex, anemia, fibrinogen levels, hypergammaglobulinemia, plasma viscosity, and reflects disease activity of the past few weeks [4], while C-reactive protein (CRP) is less confounded by these factors, and reflects more short-term changes in disease activity [5]. DAS28 using CRP (DAS28-CRP) was developed by the modification of DAS28-ESR, which had previously been developed by modification of the DAS [3]. DAS28-CRP and DAS28-ESR have been considered comparable and interchangeable when assessing RA patients, but the DAS28-CRP is not as well established as the DAS28-ESR, because its validity is inferred by comparison with DAS28-ESR [6,7]. Studies have not shown

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similar results on comparison between DAS28-CRP and DAS28-ESR in assessing RA activity and treatment response.

Comparative studies between DAS28-CRP and DAS28-ESR have shown inconsistent results when classifying RA activity and determining EULAR response criteria [6-16]. This disparity may be due to small sample sizes, low statistical power, and/or clinical heterogeneity. Therefore, in order to overcome the limitations of individual studies, resolve inconsistencies, and increase precision, we performed a meta-analysis. The present study aimed to compare DAS28-CRP with DAS28-ESR in assessing RA activity and determining EULAR response criteria, mean levels of DAS28-CRP and DAS28-ESR in RA patients, and correlation coefficients between DAS28-CRP and DAS28-ESR using the meta-analysis approach.

## MATERIALS AND METHODS

### Identification of eligible studies and data extraction

We performed a literature search for studies that examined the comparison between DAS28-CRP and DAS28-ESR in RA patients. The PubMed, EMBASE, and Cochrane databases were searched to identify all available articles (up to July 2015). The following key words and subject terms were used in the search: "DAS28," "correlation," "activity," "response criteria," "rheumatoid arthritis," and "RA." All references cited were also reviewed to identify additional studies not indexed by the above-mentioned electronic databases. Studies were considered eligible if: (1) they provided data on levels of DAS28-CRP and DAS28-ESR in RA patients, (2) they provided data on the correlation coefficient of DAS28-CRP and DAS28-ESR, or (3) they provided data on the comparison between DAS28-CRP and DAS28-ESR in assessing RA activity [3] or determining EULAR response criteria [2]. Response according to the EULAR response criteria was categorized as good (improvement  $> 1.2$  and current DAS28  $\leq 3.2$ ), moderate (improvement  $> 0.6$  to  $\leq 1.2$  and current DAS28  $\leq 5.1$ ; or improvement  $> 1.2$  and current DAS28  $> 3.2$ ), or no response (improvement  $\leq 0.6$  or improvement  $> 0.6$  to  $\leq 1.2$  and current DAS28  $> 5.1$ ) [2]. No language restriction was applied. We excluded studies if: (1) they contained overlapping or insufficient data, or (2) they were reviews. The following information was extracted from each study: first author, year of publication, country, ethnicity, number of participants, age, disease

duration, DAS28-CRP and DAS28-ESR levels, data on the comparison between DAS28-CRP and DAS28-ESR, and correlation coefficients between DAS28-CRP and DAS28-ESR. We scored the quality of each included study based on the Newcastle-Ottawa Scale [17]. The highest score was 9, and a score in the 7 to 9 range was considered to indicate high methodological quality.

### Evaluation of statistical associations

We performed meta-analyses to examine comparisons between mean levels of DAS28-CRP and DAS28-ESR in RA patients, correlation coefficients between DAS28-CRP and DAS28-ESR, and comparisons between DAS28-CRP and DAS28-ESR in assessing disease activity and determining EULAR response criteria. For continuous data, results are presented as standardized mean differences (SMDs) and 95% confidence intervals (CIs). Odds ratios (ORs) and 95% CIs were calculated for dichotomous data. Cochran's Q-statistic was used to assess within- and between-study variations and heterogeneities [18]. This heterogeneity test was used to assess the probability of the null hypothesis that all studies evaluated showed the same effect. When a significant Q-statistic ( $p < 0.10$ ) indicated heterogeneity across studies, the random effects model was used for meta-analysis, but when heterogeneity across studies was not indicated, the fixed effects model was used. This model assumes that genetic factors have similar effects on disease susceptibility across all studies and that observed variations between studies are caused by chance alone [18]. In contrast, the random effects model assumes that different studies show substantial diversity, and assesses both within-study sampling errors and between-study variances [19]. The random effects model is used in the presence of significant between-study heterogeneity. We quantified the effects of heterogeneity by using a recently developed measure, namely,  $I^2 = 100\% \times (Q - df) / Q$  [20].  $I^2$  ranges between 0% ~ 100% and represents the proportion of inter-study variability attributable to heterogeneity rather than chance.  $I^2$  values of 25%, 50%, and 75% were defined as low, moderate, and high estimates, respectively. Statistical manipulations were performed using the Comprehensive Meta-Analysis computer program (Biosta, Englewood, NJ, USA).

### Heterogeneity, sensitivity test, and publication bias

A between-study heterogeneity observed in a meta-analysis indicates variability in results across studies. A sensi-

**Table 1.** Characteristics of individual studies included in the meta-analysis

First author	Country	Ethnicity	Number of patient	Age, yr (SD)	Female, %	Disease duration, yr (SD)	Correlation coefficient	DAS28-CRP		DAS28-ESR		Data		Study quality
								(SD)	(SD)	(SD)	(SD)	Activity	Response	
Nielung, 2015 [8]	Denmark	Caucasian	75	59.7 (NA)	73	6	-	-	-	-	-	+	-	7
Sengul, 2015 [16]	Turkey	Turkish	112	55.0 (12.4)	89.3	9	0.93	-	-	-	-	-	-	8
Son, 2015 [9]	Korea	Asian	540	53.2 (12.8)	82.8	32.9 (41.2)*	0.867	3.44 (1.15)	3.65 (1.37)	+	+	+	+	9
Siemons, 2014 [10]	Netherlands	Caucasian	682	57.69 (13.85)	62.8	0~51 <sup>†</sup>	0.945	-	-	-	-	+	-	7
Tamhane, 2013 [6]	USA	African	233	52.6 (12.4)	84.6	6.6 (9.3)	-	3.90 (1.50)	4.80 (1.50)	+	+	+	-	8
Hensor, 2010 [11]	UK	Caucasian	520	57.7 (14.1)	64.2	6.0*	-	5.80 (1.31)	6.15 (1.38)	+	+	+	+	8
Crowson, 2009 [12]	USA	Caucasian	2,417	50.7 (12.3)	81.5	NA	0.96	5.71 (1.84)	6.18 (1.98)	-	-	-	-	7
Wells, 2009 [13]	Canada	Caucasian	752	50.8 (12.7)	77.2	8.5 (7.1)	-	-	-	-	-	-	+	8
Castrejón, 2008 [7]	Spain	Caucasian	220	51 (16)	76.4	5.1 (2.9)	0.91	-	-	-	-	+	-	7
Inoue, 2007 [14]	Japan	Asian	6,729	60 (NA)	82.1	9	0.946	-	-	-	-	-	-	8
Matsui, 2007 [15]	Japan	Asian	3,073	61.1 (11.4)	84.1	13.5 (10.6)	0.945	3.59 (1.25)	4.31 (1.32)	+	+	+	+	7

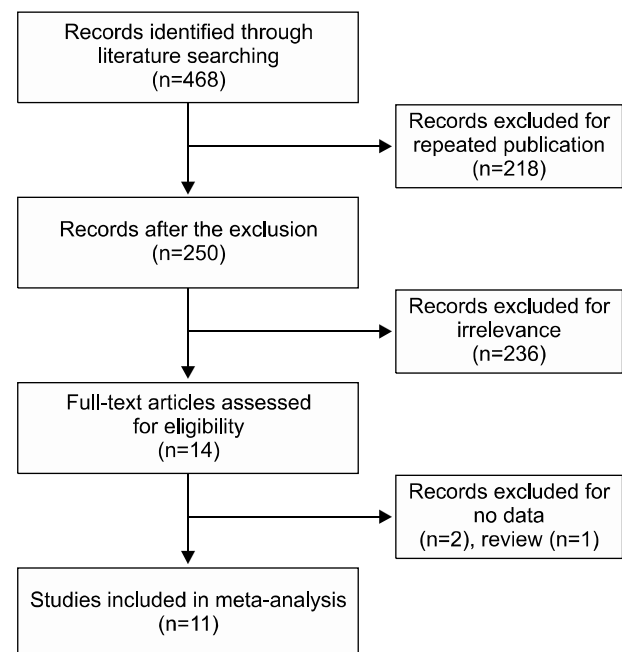
SD: standard deviation, DAS: disease activity score, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, NA: not available, +: presence, -: absence. \*months, <sup>†</sup> range.

tivity test was performed to assess the influence of each individual study on the pooled OR by omitting each study individually. While funnel plots are often used to detect publication bias, they require diverse study types of varying sample sizes, and the interpretation of the plots involves subjective judgment. Considering this, we evaluated publication bias using Egger's linear regression test [21], which measures funnel plot asymmetry using a natural logarithm scale of ORs.

## RESULTS

### Studies included in the meta-analysis

We identified 468 studies using electronic and manual searching methods. Two hundred and eighteen studies were excluded due to repeated publication, and 236 were excluded due to irrelevance, and thus 14 of these were selected for full-text review based on the title and abstract. Three of these were excluded, because they had no data, or were a review. Thus, a total of 11 articles including 15,353 RA patients met the inclusion criteria [6-16] (Table 1, Figure 1). Seven of these studies provided data on comparisons between DAS28-CRP and DAS28-ESR based on RA activity, and four of these studies provided data on comparisons between DAS28-CRP and DAS28-ESR in determining EULAR response criteria. Five examined the mean levels of both DAS28-CRP and DAS28-ESR, and 7 studies provided the correlation coefficient of

**Figure 1.** Flow diagram of study selection process.

DAS28-CRP and DAS28-ESR in RA patients. The quality assessment score of each study ranged from 7 to 9, indicating high methodological quality. Table 1 shows the characteristic features of the studies' participants as well as the studies' reported quality assessments.

### Meta-analysis of comparison between DAS28-CRP and DAS28-ESR in assessing rheumatoid arthritis activity and determining EULAR response criteria

The number of patients in each disease activity group evaluated by DAS28-CRP and DAS28-ESR were compared. A higher number of patients were classified as having remission or low disease activity when using DAS28-CRP than when using DAS28-ESR (OR=1.869, 95% CI=1.180~2.959,  $p=0.008$ ; OR=1.411, 95% CI=1.256~1.586,  $p=7.0 \times 10^{-8}$ ) (Table 2, Figure 2). However, there was no difference between DAS28-CRP and DAS28-ESR regarding the number of patients classified as having moderate disease activity. In contrast, a lower number of patients were classified as having high disease activity when using DAS28-CRP than when using DAS28-ESR (OR=0.534, 95% CI=0.388~0.734,  $p=1.1 \times 10^{-4}$ ) (Table 2, Figure 2).

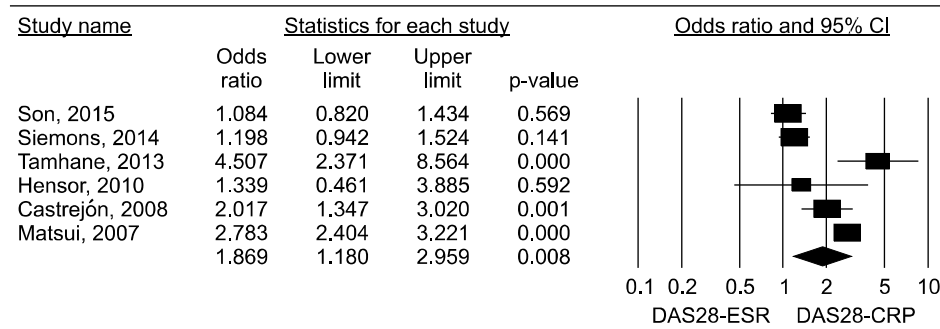
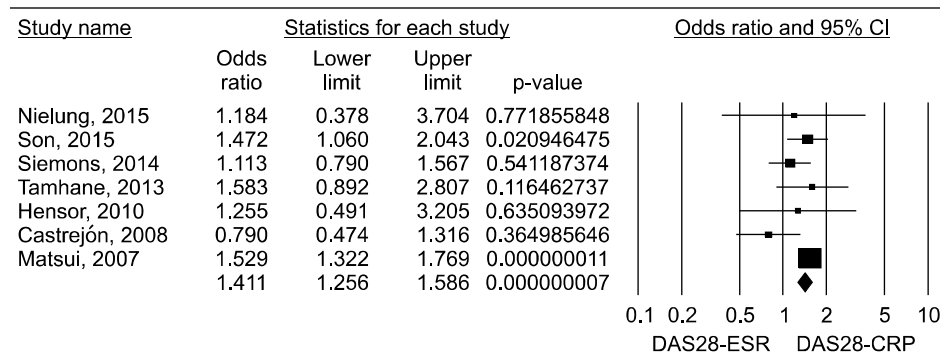
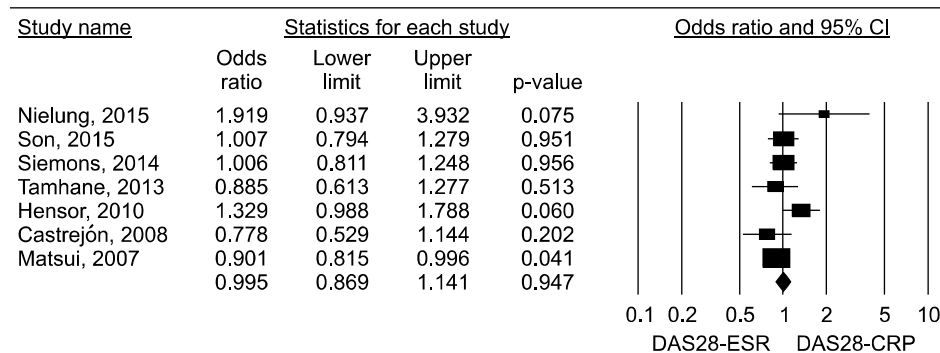
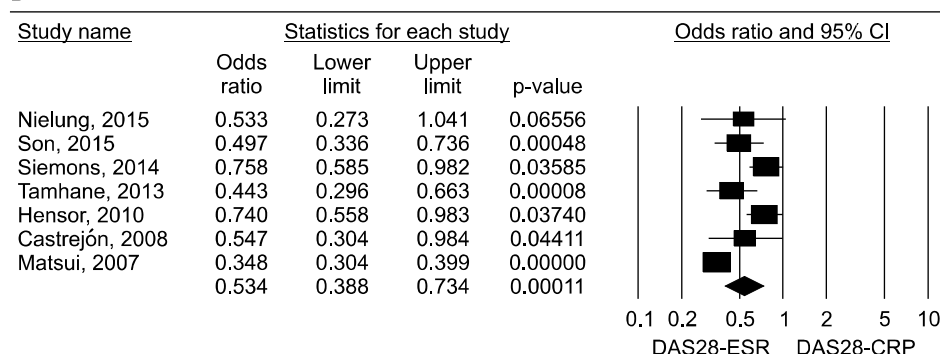
On stratification by ethnicity, a lower number of patients were classified as having high disease activity when using DAS28-CRP than when using DAS28-ESR in Caucasian patients (OR=0.712, 95% CI=0.598~0.849,  $p=1.5 \times 10^{-4}$ ) and in Asian patients (OR=0.396, 95% CI=0.283~0.554,  $p=6.0 \times 10^{-8}$ ) (Table 2).

The numbers of patients in each response group as categorized by EULAR response criteria using DAS28-CRP and EULAR response criteria using DAS28-ESR were compared. A higher number of patients were classified as showing a good response when EULAR response criteria were determined using DAS28-CRP than when the criteria were determined using DAS28-ESR (OR=1.390, 95% CI=1.183~1.632,  $p=6.10 \times 10^{-5}$ ) (Table 3, Figure 3). On stratification by ethnicity, this association was significant in Caucasian patients (OR=1.420, 95% CI=1.152~1.752,  $p=0.001$ ) and in Asian patients (OR=1.347, 95% CI=1.048~1.732,  $p=0.020$ ) (Table 3). However, the number of patients showing a moderate response or no response did not differ according to whether the criteria were based on DAS28-CRP or DAS28-ESR (Table 3).

**Table 2.** Meta-analysis of comparison between DAS28-CRP and DAS28-ESR according to RA activity

RA activity	Population	Number of study	Number of patient	Test of association		Test of heterogeneity			Publication bias
				OR (95% CI)	p-value	Model	p-value	I <sup>2</sup>	
Remission	Overall	6	5,268	1.869 (1.180~2.959)	0.008	R	0.000	91.9	0.636
	Caucasian	3	1,422	1.479 (0.990~0.210)	0.056	R	0.094	57.6	
	Asian	2	3,613	1.751 (0.695~4.408)	0.235	R	0.000	97.0	
	African	1	233	4.507 (2.371~8.564)	$4.3 \times 10^{-5}$	NA	NA	NA	
	Turkish	0	NA	NA	NA	NA	NA	NA	
Low	Overall	7	5,343	1.411 (1.256~1.586)	$7.0 \times 10^{-8}$	F	0.213	28.2	0.207
	Caucasian	4	1,497	1.028 (0.789~1.339)	0.839	F	0.191	0	
	Asian	2	3,613	1.520 (1.330~1.736)	$< 1.0 \times 10^{-8}$	F	0.834	0	
	African	1	233	1.583 (0.892~2.807)	0.116	NA	NA	NA	
	Turkish	0	NA	NA	NA	NA	NA	NA	
Moderate	Overall	7	5,343	0.995 (0.869~1.459)	0.947	R	0.078	47.1	0.199
	Caucasian	4	1,497	1.104 (0.836~1.459)	0.484	R	0.057	60.1	
	Asian	2	3,613	0.916 (0.835~1.005)	0.063	F	0.398	0	
	African	1	233	0.885 (0.613~1.277)	0.513	NA	NA	NA	
	Turkish	0	NA	NA	NA	NA	NA	NA	
High	Overall	7	5,343	0.534 (0.388~0.734)	$1.1 \times 10^{-4}$	R	0.000	85.7	0.210
	Caucasian	4	1,497	0.712 (0.598~0.849)	$1.5 \times 10^{-4}$	F	0.618	0	
	Asian	2	3,613	0.396 (0.283~0.554)	$6.0 \times 10^{-8}$	R	0.092	64.8	
	African	1	233	0.443 (0.296~0.663)	$7.6 \times 10^{-5}$	NA	NA	NA	
	Turkish	0	NA	NA	NA	NA	NA	NA	

DAS28: disease activity score 28, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, RA: rheumatoid arthritis, OR: odds ratio, CI: confidence interval, F: fixed effects model, R: random effects model, NA: not available.

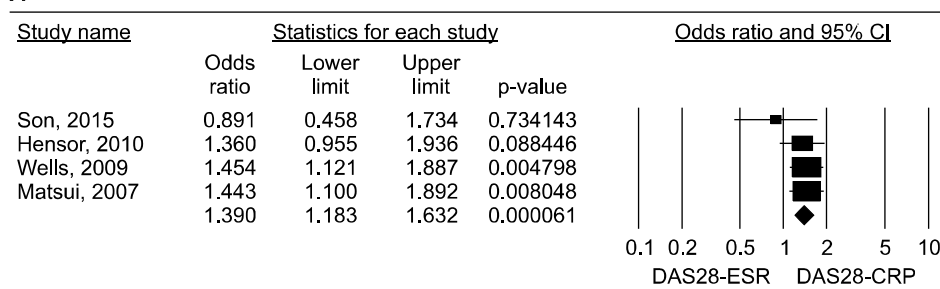
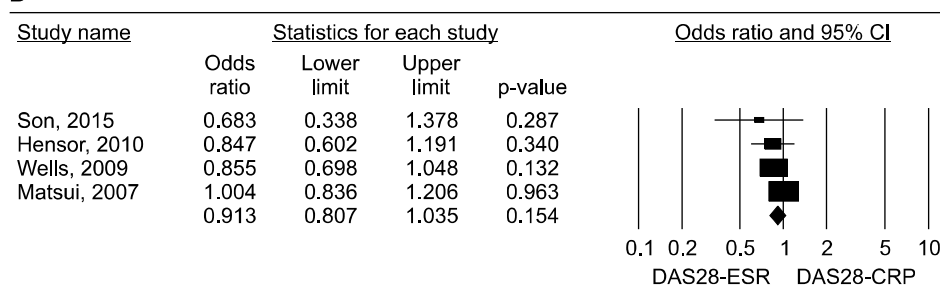
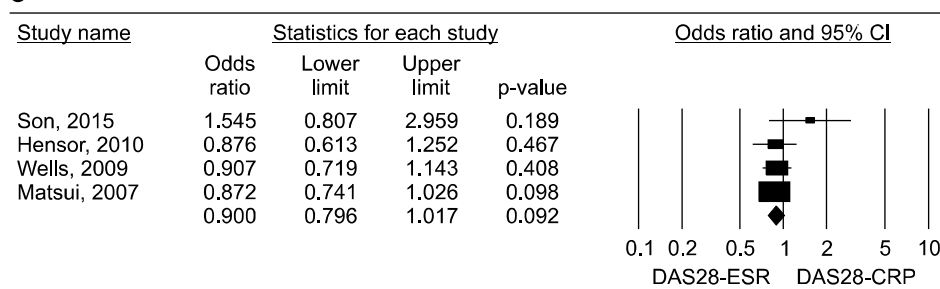
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**Figure 2.** Meta-analysis of comparison between DAS28-CRP and DAS28-ESR in assessing rheumatoid arthritis activity. DAS28: disease activity score 28, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, CI: confidence interval.

**Table 3.** Meta-analysis of comparison between DAS28-CRP and DAS28-ESR according to EULAR response criteria

EULAR response	Population	Number of study	Number of patient	Test of association		Test of heterogeneity		Publication bias	
				OR (95% CI)	p-value	Model	p-value	I <sup>2</sup>	p-value
Good	Overall	4	2,596	1.390 (1.183 ~ 1.632)	$6.1 \times 10^{-5}$	F	0.590	0	0.011
	Caucasian	2	1,036	1.420 (1.152 ~ 1.752)	0.001	F	0.763	0	
	Asian	2	1,560	1.347 (1.048 ~ 1.732)	0.020	F	0.189	42.0	
	African	0	NA	NA	NA	NA	NA	NA	
	Turkish	0	NA	NA	NA	NA	NA	NA	
Moderate	Overall	4	2,596	0.913 (0.807 ~ 1.035)	0.154	F	0.517	0	0.284
	Caucasian	2	1,036	0.853 (0.716 ~ 1.016)	0.075	F	0.962	0	
	Asian	2	1,560	0.980 (0.821 ~ 1.170)	0.823	F	0.297	7.94	
	African	0	NA	NA	NA	NA	NA	NA	
	Turkish	0	NA	NA	NA	NA	NA	NA	
No response	Overall	4	2,596	0.900 (0.796 ~ 1.017)	0.092	F	0.418	0	0.183
	Caucasian	2	1,036	0.897 (0.739 ~ 1.090)	0.275	F	0.873	0	
	Asian	2	1,560	1.061 (0.623 ~ 1.807)	0.828	F	0.094	64.4	
	African	0	NA	NA	NA	NA	NA	NA	
	Turkish	0	NA	NA	NA	NA	NA	NA	

DAS28: disease activity score 28, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, EULAR: European League Against Rheumatism, OR: odds ratio, CI: confidence interval, F: fixed effects model, NA: not available.

**A****B****C**

**Figure 3.** Meta-analysis of comparison between DAS28-CRP and DAS28-ESR in determining EULAR response criteria. DAS28: disease activity score 28, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, EULAR: European League Against Rheumatism, CI: confidence interval.

### Meta-analysis of mean differences, and correlation coefficient between DAS28-CRP and DAS28-ESR in rheumatoid arthritis

Meta-analysis showed that values of DAS28-CRP were significantly lower than those of DAS28-ESR in RA patients (SMD = -0.363, 95% CI = -0.545 ~ [-0.181],  $p = 9.4 \times 10^{-5}$ ). Meta-analysis of correlation coefficients showed a significant positive correlation between DAS28-CRP and DAS28-ESR (correlation coefficient = 0.935, 95% CI = 0.919 ~ 0.948,  $p < 1.0 \times 10^{-8}$ ). Ethnicity-specific meta-analysis revealed a significant correlation between DAS28-CRP and DAS28-ESR in Caucasians (correlation coefficient = 0.943, 95% CI = 0.915 ~ 0.961,  $p < 1.0 \times 10^{-8}$ ) and Asians (correlation coefficient = 0.927, 95% CI = 0.899 ~ 0.948,  $p < 1.0 \times 10^{-8}$ ).

### Heterogeneity, sensitivity test, and publication bias

Between-study heterogeneity was identified during the meta-analysis of comparison between DAS28-CRP and DAS28-ESR according to RA activity (Table 2). However, the meta-analytic ORs in high and low disease activity groups showed a same directionality, suggesting that the heterogeneity observed may not affect significantly the meta-analysis results. There was no heterogeneity observed in the meta-analysis of DAS28-CRP and DAS28-ESR based on EULAR response criteria (Table 3). Sensitivity analysis showed that no individual study significantly affected the pooled OR, indicating that the results of this meta-analysis are robust. Funnel plots to detect publication bias showed symmetry, and Egger's regression analysis showed no evidence of publication bias for the meta-analyses of DAS28-CRP and DAS28-ESR addressed, except for the meta-analysis for good response (Table 3).

## DISCUSSION

The original DAS was calculated based on the Ritchie articular index and 44-swollen joint count, and has been used as a tool to monitor disease activity in RA [22]. The DAS28-ESR was developed through modification of the original DAS for reasons of convenience [23], and the DAS28-CRP was proposed as a substitute for the DAS28-ESR because of the faster response of CRP to inflammation changes compared to that of ESR.

In this meta-analysis, we combined the evidence comparing DAS28-CRP and DAS28-ESR in assessing RA activity and the EULAR response criteria. This meta-analy-

sis of published studies showed a strong positive correlation between DAS28-CRP and DAS28-ESR, but values of DAS28-CRP were significantly smaller than those of DAS28-ESR in RA patients. In addition, DAS28-CRP yielded a higher number of patients classified as being in remission or with low disease activity than DAS28-ESR, while DAS28-CRP yielded a lower number of patients with high disease activity than DAS28-ESR. DAS28-CRP yielded a higher number of patients with good response than DAS28-ESR. Our meta-analysis demonstrates a significant discordance between DAS28-CRP and DAS28-ESR in evaluating RA activity and the EULAR response criteria. Although a positive correlation was found between DAS28-CRP and DAS28-ESR, this correlation does not necessarily indicate that both scores agree with each other. DAS28-CRP values have been developed to produce equivalent results to those of DAS28-ESR, but our meta-analysis supports that DAS28-CRP and DAS28-ESR values may be not interchangeable. The difference between DAS28-CRP and DAS28-ESR in assessing RA activity and EULAR response may be caused by the difference between CRP and ESR. ESR reflects disease activity of the past few weeks, whereas CRP reflects more short-term changes in disease activity [5]. Thus, CRP is more sensitive to short-term changes in disease activity. Furthermore, ESR level is more affected by several factors including sex, age, immunoglobulin levels, fibrinogen levels, rheumatoid factor, and anemia than CRP level [4].

When the cut-off values for DAS28-ESR are applied to DAS28-CRP, the disease activity could be overestimated, and the proportion of patients classified as being in remission could be increased. The DAS28-CRP may need lower cut-offs for categorizing disease activity than the DAS28-ESR. Whether the criteria of disease activity and the response criteria for DAS28-ESR could be applied to DAS28-CRP needs to be validated, because validated threshold values for DAS28-CRP have not been determined yet, and the discordance between DAS28-CRP and DAS28-ESR could result in different treatment decisions in RA patients.

The present study has some shortcomings that should be considered. First, the studies included in the meta-analysis were heterogeneous in their demographic characteristics and clinical features. The heterogeneity and confounding factors may have affected our results, which may be compounded by the limited information provided on clinical status and disease activity in the pop-

ulations involved. Second, ten studies were included in this meta-analysis, but all of these studies did not provide all type of data: The meta-analysis may be underpowered, especially in the comparison between DAS28-CRP and DAS28-ESR according to the EULAR response criteria, because only four studies were included in the meta-analysis.

Nevertheless, this meta-analysis also has its strengths. Compared to individual studies, our meta-analysis study was able to provide more accurate data on the comparison between DAS28-CRP and DAS28-ESR in assessing RA activity and determining treatment response criteria by increasing the statistical power and resolution through pooling of the results of independent analyses.

In conclusion, our meta-analysis demonstrates that DAS28-CRP correlates well with DAS28-ESR, but DAS28-CRP underestimates disease activity and overestimates response according to the EULAR response criteria compared to DAS28-ESR. Our data suggests that the DAS28-CRP needs to be evaluated using different cutoffs from those used for DAS28-ESR.

## CONFLICT OF INTEREST

The authors have no financial or non-financial conflict of interest to declare.

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