# Comparison of the Disease Activity Score Using Erythrocyte Sedimentation Rate and C-reactive Protein in African Americans with Rheumatoid Arthritis

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***ABSTRACT.*** ***Objective.*** The Disease Activity Score based on 28 joints (DAS28) has been increasingly used in clinical practice and research studies of rheumatoid arthritis (RA). Studies have reported discordance between DAS28 based on erythrocyte sedimentation rate (ESR) versus C-reactive protein (CRP) in patients with RA. However, such comparison is lacking in African Americans with RA.

***Methods.*** This analysis included participants from the Consortium for the Longitudinal Evaluation of African Americans with Early Rheumatoid Arthritis (CLEAR) registry, which enrolls self-declared African Americans with RA. Using tender and swollen joint counts, separate ESR-based and CRP-based DAS28 scores (DAS28-ESR3 and DAS28-CRP3) were calculated, as were DAS28-ESR4 and DAS28-CRP4, which included the patient's assessment of disease activity. The scores were compared using paired t-test, simple agreement and κ, correlation coefficient, and Bland-Altman plots.

***Results.*** Of the 233 included participants, 85% were women, mean age at enrollment was 52.6 years, and median disease duration at enrollment was 21 months. Mean DAS28-ESR3 was significantly higher than DAS28-CRP3 (4.8 vs 3.9; $p < 0.001$). Similarly, mean DAS28-ESR4 was significantly higher than DAS28-CRP4 (4.7 vs 3.9; $p < 0.001$). ESR-based DAS28 remained higher than CRP-based DAS28 even when stratified by age, sex, and disease duration. Overall agreement was not high between DAS28-ESR3 and DAS28-CRP3 (50%) or between DAS28-ESR4 and DAS28-CRP4 (59%). DAS28-CRP3 underestimated disease activity in 47% of the participants relative to DAS28-ESR3 and DAS28-CRP4 in 40% of the participants relative to DAS28-ESR4.

***Conclusion.*** There was significant discordance between the ESR-based and CRP-based DAS28, a situation that could affect clinical treatment decisions for African Americans with RA. (First Release Aug 15 2013; J Rheumatol 2013;40:1812–22; doi:10.3899/jrheum.121225)

*Key Indexing Terms:*
DISEASE ACTIVITY SCORE 28 RHEUMATOID ARTHRITIS AFRICAN AMERICANS

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Rheumatoid arthritis (RA) is a chronic, systemic inflammatory autoimmune disorder principally affecting synovial tissue of the joints and is associated with severe morbidity. To optimize outcome in RA, "treatment to target" by measuring disease activity and adjusting therapy accordingly has been recommended[1]. Various scoring mechanisms have been used to quantify RA disease activity, including the Simple Disease Activity Index[2], Clinical Disease Activity Index[3], and Disease Activity Score (DAS)[4,5,6]. Although none of these is universally accepted as the "gold standard," DAS has been increasingly used in clinical practice[7,8,9]. Initially it was derived from a set of 4 variables: Ritchie Articular Index, 44-joint count for swelling, erythrocyte sedimentation rate (ESR) by Westergren method, and patient assessment of global/general health (GH) based on a 100-mm visual analog scale[4,5,6]. Later, DAS28 was developed and validated[10,11], a score

based on a 28-joint count for tenderness and swelling, ESR, and GH. Both DAS and DAS28 are frequently used as outcome measures in clinical trials examining effects of "tight control" of RA[12,13,14,15]. Moreover, the American College of Rheumatology (ACR) 2008 and 2012 recommendations regarding treatment decisions involving biologic and nonbiologic disease-modifying antirheumatic drugs (DMARD) have included the DAS28 as one of the preferred outcome measures for its good psychometric properties (reliability, validity, responsiveness) and feasibility of use in clinical practice[16,17,18].

The CRP-based DAS28 (DAS28-CRP) was developed to substitute for the ESR-based DAS28[19], but it has not been fully validated[20,21,22] except in a study by Wells, *et al*[22]. Several studies, including Wells, *et al*[3,22,23,24,25,26], have reported higher DAS28 by ESR than by CRP, which could result in underestimating disease activity in patients with RA if only the DAS28-CRP is used. Thus, discordance between the DAS28-ESR and DAS28-CRP could lead to different clinical decisions in individual patients and may pose difficulties in comparing studies that use either DAS28-ESR or DAS28-CRP.

The studies that examined discordance between DAS28 by ESR versus CRP have been conducted predominantly on populations of Asian or European ancestry, and data on African Americans/black Africans are lacking. Further, in addition to differences with regard to tender joint count, activity limitation, and DAS28 between African Americans and whites[27,28,29,30], racial/ethnic differences exist in genetic polymorphisms that influence CRP levels[31,32]. Therefore, we compared DAS28-ESR versus DAS28-CRP in a cohort of African Americans with RA.

## MATERIALS AND METHODS

*Study population*. The participants for this analysis were selected from the Consortium for the Longitudinal Evaluation of African Americans with Early Rheumatoid Arthritis (CLEAR) registry, which is funded by the US National Institute of Arthritis and Musculoskeletal and Skin Diseases. Self-declared African Americans with a diagnosis of RA as defined by the revised (1987) ACR classification criteria[33] are enrolled in this registry. The participating institutions are the University of Alabama at Birmingham, Emory University (Atlanta, Georgia), the Medical University of South Carolina (Charleston), the University of North Carolina at Chapel Hill, and Washington University (St. Louis, Missouri).

The registry has 2 arms, one longitudinal (CLEAR I) and one cross-sectional (CLEAR II). Patients with < 2 years disease duration were enrolled in CLEAR I (2000 to 2005) while those with any disease duration, although typically longstanding disease, were enrolled in CLEAR II (ongoing since 2006). Comprehensive demographic, clinical, and radiographic data were obtained from CLEAR I participants at the baseline visit and at 36 and 60 months from disease onset and at 1 timepoint in CLEAR II participants. The registry was approved by the Institutional Review Boards of the respective institutions. Further details of the registry can be found at http://medicine.uab.edu/rheum/70918.

*Selection of study participants*. For this analysis, data at study enrollment from both the CLEAR I and CLEAR II arms were pooled. Although DAS28 (ESR or CRP) was available at baseline for 773 participants, analysis was restricted to 233 participants (CLEAR I 113, CLEAR II 120) for whom both DAS28-ESR3 and DAS28-CRP3 were available, enabling comparison between the same participants. This was done because of limited availability of ESR values on a subset of patients as a result of CLEAR registry protocol specifications. Serum CRP measurements are not yet available for followup visits and therefore data for (post-RA onset) 36-month and 60-month visits of CLEAR I were not included in our analysis.

*Outcome measures*. Four (standard) outcome measures were calculated[34] for our study (Table 1). Although the original DAS28 was developed using GH, patient assessment of disease activity was used in the CLEAR study because it has been included in a core set of variables and has been used as a substitute for GH[21,34]. Physician global assessment of a patient's general health/disease activity was not measured in the CLEAR study. Hereafter, the term DAS28-ESR (i.e., without any suffix of 3 or 4) is used to address DAS28-ESR generally; this is also true for DAS28-CRP. When applicable, the suffix "3" or "4" has been added to specify whether the DAS28 is calculated using 3 or 4 variables.

When enrollment into CLEAR I began, the DAS28 had not yet been widely accepted as a disease activity measure, so the Joint Alignment and Motion measure was used, which includes the tender and swollen joint counts found in the DAS28. For the same reason, DAS28-ESR4 and DAS28-CRP4 were not available for CLEAR I participants because patient global assessment of disease activity was not available to calculate the 4 variable-based scores. Serum CRP was measured by a high-sensitivity immunometric assay (hsCRP; Immulite 2000 Diagnostic Products). ESR was measured by the Westergren method.

Age and sex have been shown to influence ESR, and therefore DAS28 could also be affected[35,36]. We therefore calculated additional DAS28-CRP4 measures as suggested by Hensor, *et al*[37] (Table 1). Hensor, *et al* derived the modified formula by regressing 0.7*ln(ESR) onto ln(CRP+1), while the age-sex based formula was derived by regressing 0.7*ln(ESR) onto age (at enrollment), sex, and ln(CRP+1); thus deriving 2 definitions: unadjusted and adjusted for age and sex. Using the same strategy, we derived 2 additional study data-specific DAS28-CRP4 measures unadjusted and adjusted for age and sex (Table 1). Throughout this article, the DAS28-CRP4 refers to the standard measure unless specified to be Hensor, *et al* or a study data-specific measure.

*Statistical analysis*. Continuous variables were reported using means (SD) and/or medians (first and third quartiles). Paired data for continuous variables such as DAS28-ESR versus DAS28-CRP were compared using paired t-tests and Pearson correlation coefficient.

In addition to comparing continuous measures, agreement (concordance) between the categorized (4 disease activity levels) DAS28-ESR versus DAS28-CRP was also examined using simple agreement (categorical-distance scoring) and Cohen's simple[38] κ. For disease activity categorization, the conventional cutoffs were high: > 5.1, moderate: > 3.2 to 5.1, low: 2.6 to ≤ 3.2, and remission < 2.6[39,40]. In addition, we used cutoffs suggested by Inoue, *et al*[26] (4.1, 2.7, and 2.3) and Castrejón, *et al*[20] (4.9, 3.8, and 2.3) for comparing agreement for various DAS28-CRP measures with the standard DAS28-ESR. Thus, agreement between the standard DAS28-ESR3 was compared with the standard DAS28-CRP3 across the 3 different cutoff categories (conventional; Inoue, *et al*; and Castrejón, *et al*). Agreement between the standard DAS28-ESR4 was compared with 5 DAS28-CRP4 measures (Table 1) across the 3 different cutoff categories. Initially these agreements were examined by applying the cutoffs to both DAS28-ESR and DAS28-CRP simultaneously, i.e., these measures were categorized using the same cutoffs. In addition, agreement was also examined by applying conventional cutoffs to the standard DAS28-ESR4 while applying the newly suggested Inoue, *et al*[26] and Castrejón, *et al*[20] cutoffs to DAS28-CRP4.

Bland-Altman plots[41] were constructed to examine agreement between the DAS28 measures by plotting the mean DAS28 (ESR and CRP based) scores (X axis) against the difference of the scores (Y axis). In the Bland-Altman plot, if most of the data points lay within mean ± 2 SD

*Table 1*. Outcome measures used in the study.

| Outcome Measures | Formula/definition |
|---|---|
| Standard | |
| DAS28-ESR3 | [0.56*sqrt(Tender) + 0.28*sqrt(Swollen) + 0.70*ln(ESR)]*1.08 + 0.16 |
| DAS28-ESR4 | 0.56*sqrt(Tender) + 0.28*sqrt(Swollen) + 0.70*ln(ESR) + 0.014*(VAS) |
| DAS28-CRP3 | [0.56*sqrt(Tender) + 0.28*sqrt(Swollen) + 0.36*ln(CRP+1)]*1.10 + 1.15 |
| DAS28-CRP4 | 0.56*sqrt(Tender) + 0.28*sqrt(Swollen) + 0.36*ln(CRP+1) + 0.014*(VAS) + 0.96 |
| Hensor, *et al*[37] | |
| Unadjusted[a] DAS28-CRP4 | 0.56*sqrt(Tender) + 0.28*sqrt(Swollen) + 0.292*ln(CRP+1) + 0.014*(VAS) + 1.523 |
| Adjusted[b] DAS28-CRP4 | 0.56*sqrt(Tender) + 0.28*sqrt(Swollen) + 0.288*ln(CRP+1) + 0.014*(VAS) + 0.003*(Age) + 0.159 (if female) + 1.238 |
| Current study data-specific | |
| Unadjusted[a] DAS28-CRP4 | 0.56*sqrt(Tender) + 0.28*sqrt(Swollen) + 0.1918*ln(CRP+1) + 0.014*(VAS) + 2.086 |
| Adjusted[b] DAS28-CRP4 | 0.56*sqrt(Tender) + 0.28*sqrt(Swollen) + 0.1878*ln(CRP+1) + 0.014*(VAS) + 0.0073*(Age) + 0.2501 (if female) + 1.49843 |

[a] Unadjusted for age and sex. [b] Adjusted for age and sex. DAS: disease activity score; ESR: erythrocyte sedimentation rate; Tender: 28 tender joint count; Swollen: 28 swollen joint count; CRP: C-reactive protein, high sensitivity; VAS: visual analog scale, self-assessed patient global assessment of disease activity on a VAS of 0 to 100 mm.

(limits of agreement), the measures were said to be interchangeable provided the differences within the SD were not clinically important. However, in our study the differences within the 2 SD were deemed clinically important: a difference of > 0.6 between DAS28-ESR and DAS28-CRP was considered as greater than measurement error and a difference > 1.2 as clinically significant[39,42,43,44]. Therefore, instead of using mean and SD, cutoffs of (±) 0.6 and (±) 1.2 were used to denote the limits of agreement in the plots.

Statistical significance was set at 0.05 (2-tailed).

## RESULTS

Overall, 233 participants were included for analysis, of whom 198 (84.6%) were women; all were African Americans. Mean age at enrollment was 52.6 years and mean age at RA onset was 46 years (Table 2). Median disease duration at enrollment was 1.8 years. No significant differences were found between the included (analyzed) and excluded participants (n = 540) with regard to age at

*Table 2*. Sociodemographic and clinical characteristics of the CLEAR participants for whom both DAS28-ESR and DAS28-CRP were available. DAS28 form and therefore VAS were available only for CLEAR II participants.

| Characteristic | N | Mean (SD) | Median (Q1–Q3) |
|---|---|---|---|
| Age at enrollment, yrs | 233 | 52.6 (12.4) | 51.9 (45.5–59.0) |
| Age at RA onset, ys | 233 | 46.0 (13.7) | 45.3 (37.3–53.7) |
| Disease duration at enrollment, yrs | 233 | 6.6 (9.3) | 1.8 (0.8–9.3) |
| ESR, mm/hr | 233 | 44.3 (27.8) | 40 (22–61) |
| hsCRP, mg/dl | 233 | 17.1 (34.9) | 5.6 (2.0–19.4) |
| Tender joint count (DAS28) | 233 | 7.5 (7.7) | 5 (1–12) |
| Swollen joint count (DAS28) | 233 | 5.7 (6.4) | 4 (1–8) |
| HAQ score | 233 | 1.4 (0.8) | 1.5 (0.9–1.9) |
| Patient's general health (VAS, 0–100 mm) | 120 | 49.1 (27.0) | 51 (28–68) |
| DAS28 | | | |
| Using 3 variables: tender, swollen, ESR/CRP | | | |
| DAS28-ESR3 (both CLEAR I and II) | 233 | 4.8 (1.5) | 4.7 (3.7–5.9) |
| DAS28-CRP3 (both CLEAR I and II) | 233 | 3.9 (1.5) | 3.8 (2.7–5.1) |
| Paired t-test, p value* | | < 0.001 | — |
| Using 4 variables: tender, swollen, ESR/CRP, VAS | | | |
| DAS28-ESR4 (only CLEAR II) | 120 | 4.7 (1.4) | 4.6 (3.6–5.7) |
| DAS28-CRP4 (only CLEAR II) | 120 | 3.9 (1.4) | 3.9 (2.8–4.9) |
| Paired t-test, p value* | | < 0.001 | — |

* P value for comparing means. CLEAR: Consortium for the Longitudinal Evaluation of African Americans with Early Rheumatoid Arthritis registry; Q1: first quartile; Q3: third quartile; RA: rheumatoid arthritis; ESR: erythrocyte sedimentation rate by Westergren method; hsCRP: high-sensitivity C-reactive protein; DAS28: 28-joint Disease Activity Score; HAQ: Health Assessment Questionnaire; VAS: visual analog scale, self-assessed patient global assessment.

enrollment or RA onset, disease duration, tender/swollen joints, Health Assessment Questionnaire score, rheumatoid factor (RF), anticyclic citrullinated peptide (anti-CCP, anti-citrullinated protein) antibody, and HLA-DRB1 shared epitope associated with RA.

*DAS28 as a continuous variable*. When all the participants (n = 233) were included in the analysis, mean DAS28-ESR3 was significantly higher than DAS28-CRP3 (4.8 vs 3.9; $p < 0.001$; Table 2). The mean DAS28-ESR4 was also significantly higher than the mean DAS28-CRP4 (4.7 vs 3.9; $p < 0.001$). When DAS28-ESR3 and DAS28-CRP3 were compared, an absolute difference of ≤ 0.6 was observed in 65 (27.9%), > 0.6 in 110 (47.2%), and > 1.2 in 58 (24.9%) participants; the corresponding values for DAS28-ESR4 vs DAS28-CRP4 comparison were 42 (35.0%), 61 (50.8%), and 17 (14.2%). The Bland-Altman plots (Figures 1A and 1B) showed similar findings. The plots reveal that differences between DAS28-ESR and DAS28-CRP were positive for most of the participants, i.e., DAS28-ESR was higher than DAS28-CRP. DAS28-ESR3 was higher than DAS28-CRP3 in 91.0% (212/233) participants and DAS28-ESR4 was higher than DAS28-CRP4 in 88.3% (106/120) participants. The plots also show that the agreement between DAS28-ESR3 and DAS28-CRP3 was lower than the agreement between DAS28-ESR4 and DAS28-CRP4. The correlation of DAS28-ESR3 with DAS28-CRP3 was high (Pearson correlation coefficient, $r = 0.92$; $p < 0.001$); a similarly high correlation was observed for DAS28-ESR4 with DAS28-CRP4 ($r = 0.92$, $p < 0.001$).

Mean DAS28-ESR vs DAS28-CRP were also examined by stratifying on factors that could be associated with disease activity such as age (< 40, 40 to < 50, 50 to < 60, and 60+ years), sex, disease duration (< 12, 12 to < 36, 36 to < 60, and 60+ months), RF (positive, negative), anti-CCP antibody (positive, negative), and HLA-DRB1 shared epitope (present vs absent; data available from author on request). In the interstrata comparison, DAS28-ESR3 was significantly higher than DAS28-CRP3 ($p < 0.001$) for all the factors except for disease duration 36 to < 60 months, where DAS28-ESR3, although higher than DAS28-CRP3, was not significantly different (3.7 vs 3.3; $p = 0.08$). In the intrastrata (i.e., within the strata) comparison of DAS28-ESR3 vs DAS28-CRP3, the scores did not differ significantly from each other except for sex (unpaired t-test, $p = 0.01$) and disease duration (ANOVA, $p = 0.003$) for DAS28-ESR3. Similarly in the interstrata comparison, DAS28-ESR4 was significantly higher than DAS28-CRP4 for all the factors except for disease duration 36 to < 60 months (paired t-test, $p = 0.1$). In the intrastrata comparison of DAS28-ESR4 and DAS28-CRP4, the scores did not differ significantly from each other except for RF (unpaired t-test, $p = 0.05$) for DAS28-ESR4 only.

The study data-specific modified (unadjusted for age-sex) DAS28-CRP4 had a mean of 4.7 (SD 1.3) and the age-sex adjusted DAS28-CRP4 had a mean of 4.8 (SD 1.3); no significant difference was found when compared to DAS28-ESR4 (mean 4.7, SD 1.4) with $p = 0.24$ and $p = 0.10$, respectively. The Hensor, *et al* modified (unadjusted for age-sex) DAS28-CRP4 had a mean of 4.4 (SD 1.4)[37] and the age-sex adjusted DAS28-CRP4 had a mean of 4.3 (SD 1.4); statistical significance was observed for both with $p < 0.001$.

*DAS28 as a categorical variable*. Agreement between the standard DAS28-ESR and standard DAS28-CRP with regard to 4 disease activity categories is presented in Table 3. When DAS28-ESR3 versus DAS28-CRP3 were compared, agreement with regard to DAS28 categories was observed in 117 participants (50.2%) while 110 (47.2%) were underestimated and 6 (2.6%) were overestimated by DAS28-CRP3; overall agreement was 50.2% with $\kappa = 28.3\%$. Similarly, when DAS28-ESR4 versus DAS28-CRP4 were compared, 71 participants (59.2%) had an agreement while 48 (40.0%) were underestimated and only 1 (0.9%) was overestimated by DAS28-CRP4; overall agreement was 59.2% with $\kappa = 40.5\%$.

Figure 2 shows the comparison of simple agreement and κ between the standard DAS28-ESR3 and the standard DAS28-CRP3 for various cutoffs. The agreement, κ, and underestimation (by DAS28-CRP3) were more or less the same across all cutoffs. Figures 3A and 3B show simple agreement and κ between the standard DAS28-ESR4 and various DAS28-CRP4 measures. Across all the cutoff categories, simple agreement and κ were higher for the study data-specific measures than those for the standard or Hensor, *et al* measures. The agreements ranged from 76% to 84% for the study data-specific DAS28-CRP4 measures across various cutoffs while they ranged from 53% to 59% for the standard measures (Figure 3A); the differences between the study data-specific and the standard measures were significant across all the cutoffs.

Using conventional cutoffs, the proportion of participants with underestimation of disease activity by DAS28-CRP4 decreased from 40% in the standard DAS28-CRP4 to 8% in the (age-sex) unadjusted study data-specific measure and to 6% in the adjusted study data-specific measure (Figure 3C). A similar decrease in underestimation was observed in the Inoue, *et al* and Castrejón, *et al* cutoffs also (Figure 3C).

Simple agreement and κ between DAS28-ESR4 and DAS28-CRP4 were also examined by applying conventional cutoffs to the standard DAS28-ESR4 (categorizing it into 4 disease activity levels) while applying Inoue, *et al* and Castrejón, *et al* cutoffs to DAS28-CRP4 (standard; Hensor, *et al*; and study data-specific; data available from author on request). In contrast to the above results, agreements for the study data-specific measures were lower than those for the standard and Hensor, *et al* measures. Highest agreement was observed for the standard DAS28-CRP4 (73%) using the Inoue cutoffs. For the study data-specific DAS28-CRP4

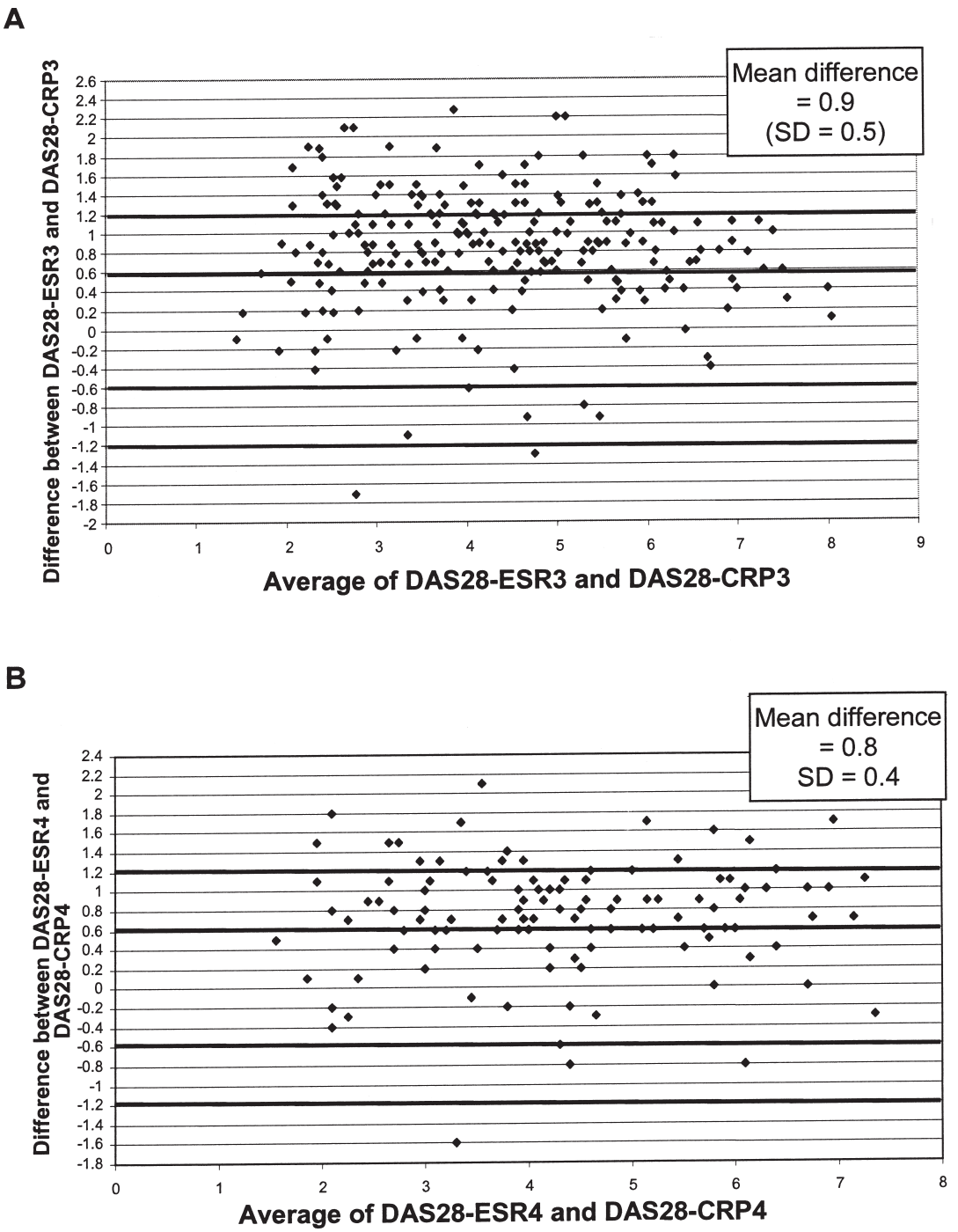


*Figure 1*. A. Bland-Altman plot analysis of DAS28-ESR3 versus DAS28-CRP3, n = 233. B. Bland-Altman plot analysis of DAS28-ESR4 versus DAS28-CRP4, n = 120. A difference of > 0.6 between DAS28-ESR and DAS28-CRP was considered as greater than measurement error and a difference > 1.2 as clinically significant. DAS: Disease Activity Score; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

measures (both unadjusted and adjusted for age-sex), simple agreement was only 50% when Inoue, *et al* cutoffs were applied and 66% with the Castrejón, *et al* cutoffs. With the Inoue, *et al* cutoffs, simple κ was 60% for the standard DAS28-CRP4 and 33% for the (age-sex) unadjusted and adjusted study data-specific DAS28-CRP4. With the Castrejón, *et al*, cutoffs, the κ were 28%, 51%, and 50%, respectively. Thus, overall these agreements were lower than the agreement observed for the study data-specific DAS28-CRP4 measures (range was 76% to 84% across

*Table 3*. Agreement between DAS28-ESR and DAS28-CRP by disease activity categories.

| DAS28-CRP | Disease Categories | | | | Total |
|---|---|---|---|---|---|
| | High, > 5.1 | Moderate, ≥ 3.2 to ≤ 5.1 | Low, ≥ 2.6 to < 3.2 | Remission, < 2.6 | |
| | | | DAS28-ESR3 | | |
| | n = 93 | n = 105 | n = 22 | n = 13 | n = 233 |
| DAS28-CRP3 | | | | | |
| High | **50** | 3 | 0 | 0 | 53 |
| Moderate | *43* | **52** | 2 | 1 | 98 |
| Low | *0* | *30* | **3** | 0 | 33 |
| Remission | *0* | *20* | *17* | **12** | 49 |
| | | | DAS28-ESR4 | | |
| | n = 43 | n = 57 | n = 11 | n = 9 | n = 120 |
| DAS28-CRP4 | | | | | |
| High | **27** | 0 | 0 | 0 | 27 |
| Moderate | *16* | **35** | 0 | 1 | 52 |
| Low | *0* | *14* | **1** | 0 | 15 |
| Remission | *0* | *8* | *10* | **8** | 26 |

Self-assessed patient global assessment of disease activity on a visual analog scale was not included while calculating DAS28-ESR3 and DAS28-CRP3 and was included for DAS28-ESR4 and DAS28-CRP4. Numbers in boldface indicate agreement between the 2 scores. Numbers in italics are the numbers of patients for whom disease activity would be "underestimated" if DAS28-CRP were used instead of DAS28-ESR. DAS28: 28-joint Disease Activity Score; ESR: erythrocyte sedimentation rate by Westergren method; CRP: C-reactive protein.

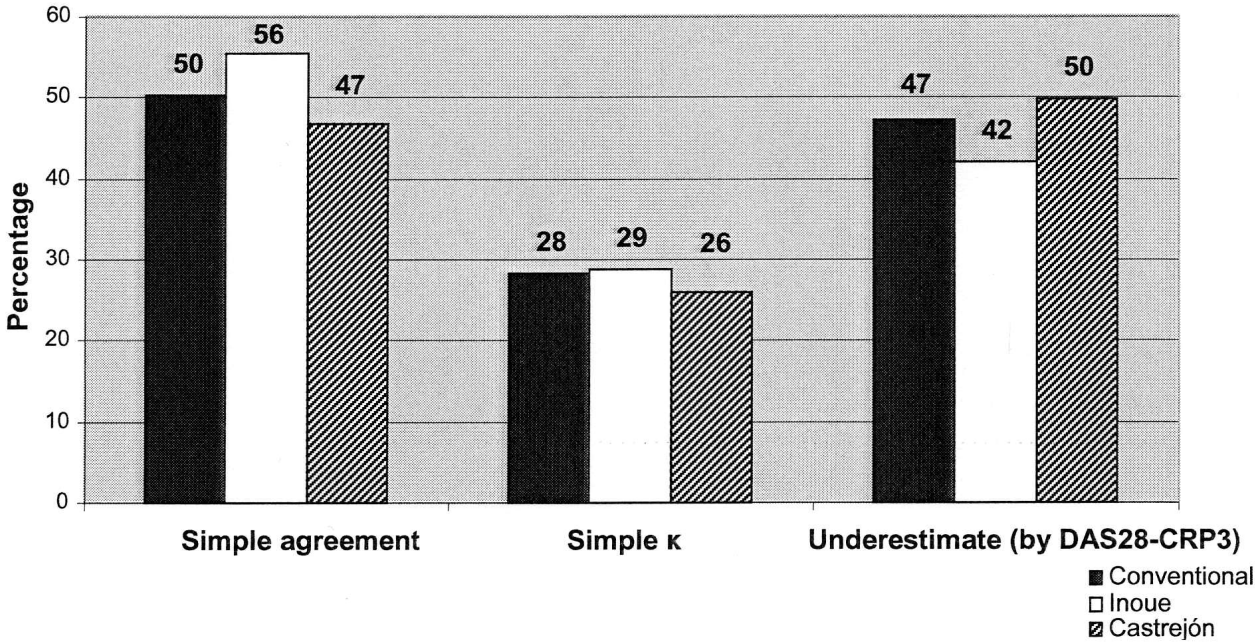


*Figure 2*. Agreement between the standard DAS28-ESR3 and the standard DAS28-CRP3 measures by various cutoff values for disease activity categories [conventional (5.1, 3.2, 2.6)[39,40]; Inoue, *et al* (4.1, 2.7, 2.3)[26]; and Castrejón, *et al* (4.9, 3.8, 2.3)[20]]. DAS: Disease Activity Score; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

various cutoffs, Figure 3A) when the same cutoffs were applied to both DAS28-ESR4 and DAS28-CRP4. Mixed results were obtained for simple κ.

## DISCUSSION

We observed that even though DAS28-ESR and DAS28-CRP were highly positively correlated, DAS28-ESR

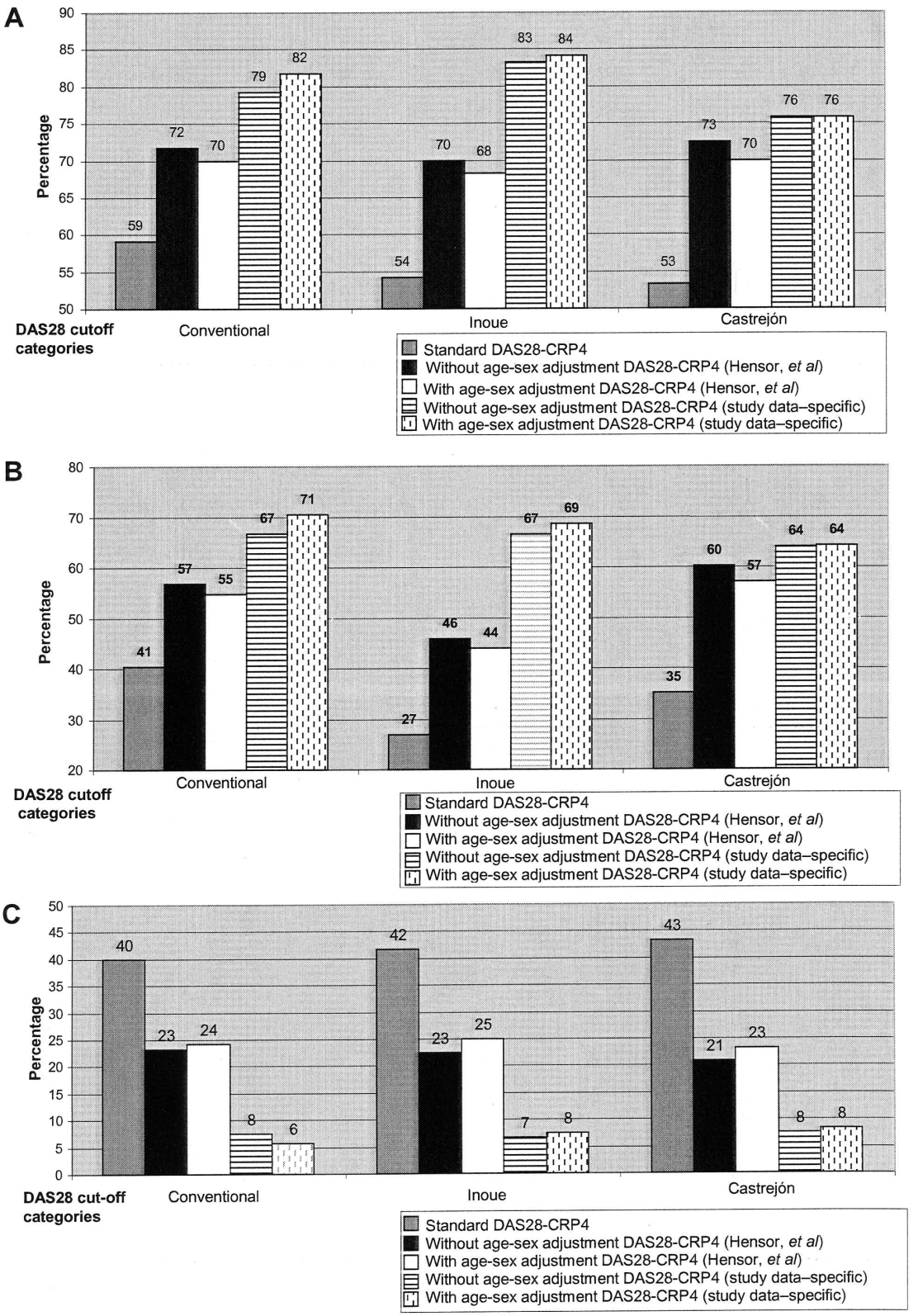


*Figure 3*. A. Comparison of simple agreement between the standard DAS28-ESR4 and various DAS28-CRP4 measures by different cutoff values for disease activity categories. B. Comparison of simple κ between the standard DAS-ESR4 and various DAS28-CRP4 measures by different cutoff values for disease activity categories. C. Underestimation by DAS28-CRP4 relative to DAS28-ESR4 by different cutoff values for disease activity categories. Cutoffs for each panel were conventional (5.1, 3.2, 2.6)[39,40]; Inoue, *et al* (4.1, 2.7, 2.3)[26]; and Castrejón, *et al* (4.9, 3.8, 2.3)[20]. DAS: Disease Activity Score; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

was significantly higher than DAS28-CRP, both with and without patient global assessment of disease activity in the formula. Thus, in comparison with DAS28-ESR, DAS28-CRP "underestimated" disease activity. DAS28-ESR remained higher than DAS28-CRP even after stratifying on variables such as age, sex, disease duration, RF, anti-CCP antibody, and shared epitope. Although overall agreement and κ (agreement above chance) were higher between DAS28-ESR4 and DAS28-CRP4 than between DAS28-ESR3 and DAS28-CRP3, the values were low in general. As compared to the standard measure DAS28-CRP4, the study data-specific measures (unadjusted/adjusted for age and sex) significantly improved agreement, including κ, even with conventional cutoffs.

The strong positive correlation between DAS28-ESR and DAS28-CRP observed in our study is similar to other studies[26,37,45]. However, a strong correlation does not necessarily mean the scores agree with each other[41]. A positive correlation indicates only that increase in 1 variable is also accompanied by increase in another variable. The differences between the 2 scores could be examined in 2 ways: (1) as a continuous measure comparing means/medians of DAS28-ESR and DAS28-CRP in the same participants; or (2) examining the DAS28 categories (high, moderate, low, and remission) and then comparing them with regard to agreement and κ. In this analysis, significant (both clinically and statistically) differences were observed between DAS28-ESR and DAS28-CRP for both the continuous and categorical measures. Mean scores differed significantly and both overall agreement and κ were low. The finding of discrepant scores with DAS28-ESR being higher than DAS28-CRP is similar as observed in other studies[3,23,24,25,26,37,46,47]; in contrast, Wells, *et al*[22] found a high degree of agreement between the scores. Further, in our study, the differences between DAS28-ESR and DAS28-CRP remained significant even when stratified by age, sex, disease duration, RF, anti-CCP antibody, and shared epitope, with occasional exceptions due to chance. In the Matsui, *et al*[23], study, higher values with DAS28-ESR4 were also observed when stratified by age, sex, and disease duration; in particular, the influence of age and sex has also been evaluated in detail in other studies[35,37].

In our study, DAS28-CRP3 underestimated disease activity in 47% of participants and DAS28-CRP4 in 40% when compared to DAS28-ESR3 and DAS28-ESR4, respectively. Matsui, *et al*[23] also found 43% of their study participants being underestimated by DAS28-CRP4. In contrast, Hensor, *et al*[37] found that only 9% of their early RA participants (disease duration ≤ 12 mo) were underestimated by DAS28-CRP4; also overall simple agreement (88.5%) and κ (70.2%) were high in that study. When analysis was restricted to such early RA participants in our study (n = 76), overall simple agreement between DAS28-ESR4 and DAS28-CRP4 remained low at 51.3% with simple κ = 28.9%.

To make the DAS28-ESR and DAS28-CRP equivalent, it has been suggested that either the definition/formula of the standard DAS28-CRP be changed or new disease activity cutoffs be applied to categorize the scores into high, moderate, low, and remission[20,23,26,37]. Such a categorization of DAS28 is used for clinical decisions regarding treatment initiation/switching or for curtailing the current treatment. We developed the study data-specific definitions in this analysis and examined how these and Hensor, *et al*[37] definitions (with and without age-sex adjustment) would influence agreement between DAS28-ESR and DAS28-CRP. These agreements were examined using 3 cutoffs for disease activity: conventional, those suggested by Inoue, *et al*[26], and those suggested by Castrejón, *et al*[20]. The new study data-specific measures (both unadjusted and adjusted for age-sex) of DAS28-CRP4 significantly improved overall agreement and κ with DAS28-ESR4 as compared to (standard) DAS28-CRP4. This indicates that a change in the definition (i.e., conversion/multiplying factor in the formula) of DAS28 could be advantageous. In contrast to the Hensor, *et al*[37] finding of the age-sex adjusted DAS28-CRP4 measure having greater agreement, we observed that the (age-sex) unadjusted and adjusted study data-specific measures were almost the same with regard to simple agreement, κ, and underestimation by DAS28-CRP4. Also, the study data-specific measures had higher agreement and κ than those for the Hensor, *et al*[37] measures. However, it should be noted that although study data-specific measures were constructed using the same strategy as that by Hensor, *et al*, the constants and multipliers obtained for the DAS28-CRP4 formulae were different from those obtained in the Hensor, *et al*, study[37]. Thus, even though Hensor, *et al*, definitions improved agreement and κ, using study data-specific definitions might give an upper edge. This, in turn, leads to another dilemma of whether the study data-specific definitions could have limitations with regard to external generalizability because of different population characteristics such as age, sex, race, or disease duration, among others. Other studies[22,37] have also reported limitations in applying such cutoffs to their study participants. Therefore, a new definition for DAS28-CRP based on a variety of datasets may be needed[22,37], or one could develop different (separate for DAS28-ESR and DAS28-CRP) cutoffs for the existing definitions. To further examine this, we examined agreement by applying conventional cutoffs (2.6, 3.2, 5.1) to the standard DAS28-ESR4 (for categorizing disease activity) while applying newly suggested Inoue, *et al* (4.1, 2.7, and 2.3) and Castrejón, *et al* (4.9, 3.8, and 2.3) cutoffs to various DAS28-CRP4 measures (conventional, Hensor, *et al*, and study data-specific). The agreement was not better than that obtained by applying the same cutoffs. Whether a

new definition and/or cutoffs could increase external generalizability remains to be further examined.

Because of additional gain in agreement, Hensor, *et al*[37] have suggested use of age-sex adjusted definition for classifying patients into various DAS28 categories although not for European League Against Rheumatism responder states. In contrast, we found that (age-sex) unadjusted and adjusted study data-specific measures were at par with each other, indicating that additional variables may not be needed. One potential problem of adding more variables to the existing definition/formula of DAS28 is that it could lead to underuse of DAS28 in clinical practice. This could be due to the complexity of the formula and/or lack of data on all the variables, although age and sex of a patient are generally readily available and one can use a simple calculator or a nomogram or a computer (e.g., Microsoft Excel or a Website). Although DAS28 has been shown to be useful in monitoring disease activity[14,42,48,49] and is clinically interpretable[40], its usefulness in daily practice has been questioned[50]. Therefore, a simple modification, without age-sex adjustment, in the conversion/multiplying factor with conventional cutoffs could be the optimal strategy to make the DAS28-ESR and DAS28-CRP equivalent.

One of the limitations of our study is its relatively small sample size, especially while comparing DAS28-ESR4 and DAS28-CRP4 measures, and therefore cross-validation of the modified formulae was not done. The small sample size was due to limited availability of ESR values on a subset of patients because of CLEAR registry protocol specifications. However, the primary aim of the study was not to develop new definitions *per se* but to examine agreement between the 2 measures. Although a previous metaanalysis[51] has shown a slight advantage of ESR for later timepoints, CRP has been suggested as a better measure for multiinvestigator studies because of its stability and the ability to have serum specimens analyzed by a central laboratory, as we did in the CLEAR study[52].

Although our sample size is smaller than that used for similar studies of patients with RA who are of European or Asian ancestry, we show statistically significant differences. The CLEAR registry represents the largest group of African Americans to be analyzed. Because RA is generally considered to be less common in this racial/ethnic group compared to others, and because African Americans are a minority group underrepresented in RA research[53], our findings are of importance to the African American population and to the community of RA researchers.

No significant differences were found between the included and the excluded participants with regard to DAS28-ESR and DAS28-CRP; the means were almost the same. Therefore, inclusion of the excluded participants would not have changed the conclusions of the study, although certainly it would have added to the precision of the measurement estimates. However, the possibility of differences with regard to other unmeasured variables cannot be ruled out. Although the general findings of our study are in agreement with other studies, our study data-specific modified definitions may not be generalizable to populations other than African Americans with RA, a limitation found in other studies[37].

Despite there being a strong correlation, significant discrepancy between DAS28-ESR and DAS28-CRP exists that could lead to differences in clinical decisions regarding treatment initiation/switching or curtailing the current treatment. In addition, it may be difficult to compile or to compare results from various studies using different DAS formulae based on CRP or ESR. DAS28-CRP underestimates disease activity when conventional cutoffs are used. Significant gains with regard to improving agreement and decreasing underestimation could be achieved using a simple modification in the existing DAS28-CRP definition. However, it remains to be examined whether population-specific definitions are needed or whether a universal DAS28-CRP definition could be derived using a variety of databases, and/or whether different cutoffs for DAS28-ESR and DAS28-CRP are needed.

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