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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

INTRODUCTION—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 RA patients. 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 kappa, 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 which could impact clinical treatment decisions in African-Americans with RA.

Keywords

DAS28; Rheumatoid Arthritis; African-Americans

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory autoimmune disorder principally affecting synovial tissue of the joints and is associated with severe morbidity. For optimizing 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 (SDAI),² Clinical Disease Activity Index (CDAI),³ and Disease Activity Score (DAS).^{4–6} Although none of these is universally accepted as the “gold standard”, DAS has been increasingly used in clinical practice.^{7–9} Initially it was derived from a set of four 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 (VAS).^{4–6} Later, DAS28 was developed and validated^{10, 11} where the score was based on 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.^{12–15} Moreover, the American College of Rheumatology 2008 and 2012 recommendations regarding treatment decisions using of biologic and non-biologic disease-modifying anti-rheumatic drugs (DMARDs) have included the DAS28 as one of the preferred outcome measures for its good psychometric properties (reliability, validity, responsiveness) and feasibility of using in clinical practice.^{16–18}

The CRP-based DAS28 (DAS28-CRP) was developed to substitute for the ESR-based DAS28,¹⁹ but it has not been fully validated^{20–22} except a recent study by Wells et al;²² Several studies, including that by Wells et al,^{3, 22–26} have reported higher DAS28 by ESR than DAS28 by CRP which could result in underestimating disease activity in RA patients should one use only the DAS28-CRP. 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 previous studies that examined discordance between DAS28 by ESR vs. CRP have been conducted predominantly on populations of Asian or European ancestry and data on African-Americans/black Africans is lacking. Furthermore, in addition to differences with regard to number of tender joint count, activity limitation, and DAS28 between African-Americans and Caucasians,^{27–30} racial/ethnic differences in genetic polymorphisms that influence CRP levels exist.^{31, 32} Therefore, in this analysis we compared DAS28-ESR versus DAS28-CRP in a cohort of African-Americans with RA.

PATIENTS 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 National Institute of Arthritis and Musculoskeletal and Skin Diseases. Self-declared African Americans with a diagnosis of RA as defined by the revised (1987) American College of Rheumatology (ACR) classification criteria³³ are enrolled in this registry. The participating institutions for this registry are: the University of Alabama at Birmingham (UAB), Emory University (Atlanta, GA), the Medical University of South Carolina (Charleston), the University of North Carolina at Chapel Hill, and Washington University (St. Louis, MO).

The registry has two arms, one longitudinal (*CLEAR I*) and one cross-sectional (*CLEAR II*). Patients with <2 years disease duration were enrolled in *CLEAR I* (Year 2000 to 2005) while those with any disease duration, though typically long-standing 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 one time point 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 due to limited availability of ESR values on a subset of patients due to *CLEAR* registry protocol specifications. Serum CRP measurements are not yet available at follow-up visits and therefore data for (post-RA onset) 36-month and 60-month visits of *CLEAR I* was not included in this analysis.

Outcome measures

Four (standard) outcome measures were calculated³⁴ for this study (Table 1). Although the original DAS28 was developed using GH, patient's assessment of disease activity was used in the *CLEAR* study as it has been included in core set of variables and has been used as a substitute for GH.^{21, 34} Physician's global assessment of 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 specifying whether the DAS28 is calculated using 3 or 4 variables, respectively.

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 (JAM) was used, which includes the tender and swollen joint counts used in the DAS28. For the same reason,

DAS28-ESR4 and DAS28-CRP4 were not available for *CLEAR I* participants as patient's global assessment of disease activity was not available to calculate the 4-variables based scores. Serum CRP was measured by a high-sensitivity immunometric assay (hsCRP) (Immulite 2000 Diagnostic Products, Los Angeles, CA, USA). 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 $0.7 \cdot \ln(\text{ESR})$ onto $\ln(\text{CRP}+1)$ while age-sex based formula was derived by regressing $0.7 \cdot \ln(\text{ESR})$ onto age (at enrollment), sex, and $\ln(\text{CRP}+1)$; thus deriving two definitions: unadjusted and adjusted for age and sex. Using the same strategy, we derived two additional study-data-specific DAS28-CRP4 measures unadjusted and adjusted for age and sex (Table 1). Through out this article, the DAS28-CRP4 refers to the standard measure unless specified to be Hensor et al. or study-data-specific measure.

STATISTICAL ANALYSIS

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

In addition to comparing continuous measures, agreement (concordance) between the categorized (four disease activity levels) DAS28-ESR vs. DAS28-CRP was also examined using simple agreement (categorical-distance scoring) and Cohen's simple³⁸ kappa. For disease-activity categorization, the conventional cut-offs used 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 cut-offs 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 three different cut-off categories (conventional, Inoue et al. and Castrejón et al). While agreement between the standard DAS28-ESR4 was compared with five DAS28-CRP4 measures (Table 1) across the three different cut-off 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 cut-offs. 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 cut-offs to DAS28-CRP4.

Bland-Altman plots⁴¹ 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 Bland-Altman plot, if most of the data points lay within mean ± 2 standard deviations ("limits of agreement"), the measures are said to be interchangeable provided the differences within the standard deviations are not clinically important. However, in this study the differences within the two standard deviations 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, 42–44} Therefore, instead of the using mean and standard deviation, cut-offs of $(\pm) 0.6$ and $(\pm) 1.2$ were used to denote the limits of agreement in the plots.

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

RESULTS

Overall, 233 participants were included for analysis, of which 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 enrollment or RA onset, disease duration, tender/swollen joints, HAQ score, rheumatoid factor, anti-CCP 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), rheumatoid factors (positive, negative), anti-cyclic citrullinated peptide (CCP) antibody (positive, negative), and HLA-DRB1 shared epitope (present vs. absent) (see supplemental tables 4 and 5). In the inter-strata 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, though higher than DAS28-CRP3, was not significantly different (3.7 vs. 3.3; $p=0.08$). In the intra-strata (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 inter-strata comparison, DAS28-ESR4 was significantly higher than DAS28-CRP4 for all the factors except for disease duration 36 to <60 months (paired t-test, $p=0.10$). In the intra-

strata comparison of DAS28-ESR4 and DAS28-CRP4, the scores did not differ significantly from each other except for rheumatoid factor (unpaired t-test, $p=0.05$) for DAS28-ESR4 only.

The study-data-specific modified (unadjusted for age-sex) DAS28-CRP4 had mean of 4.7 (SD=1.3) and age-sex adjusted DAS28-CRP4 had 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 mean of 4.4 (SD=1.4) and age-sex adjusted DAS28-CRP4 had 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 four disease activity categories is presented in Table 3. When DAS28-ESR3 vs. DAS28-CRP3 were compared, agreement with regard to DAS28 categories was observed in 117 (50.2%) participants 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 vs. DAS28-CRP4 were compared, 71 (59.2%) participants 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 kappa between the standard DAS28-ESR3 and the standard DAS28-CRP3 for various cut-offs. The agreement, kappa, and underestimation (by DAS28-CRP3) was more or less the same across all cut-offs. Figures 3a and 3b show simple agreement and kappa between the standard DAS28-ESR4 and various DAS28-CRP4 measures. Across all the cut-off categories, simple agreement and kappa were higher for the study-data-specific measures than that 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 cut-offs 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 cut-offs.

Using conventional cut-offs 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% with in the adjusted study-data-specific measure (Figure 3c). Similar decrease in underestimation was observed in the Inoue et al. and Castrejón et al cut-offs too (Figure 3c).

Simple agreement and kappa between DAS28-ESR4 and DAS28-CRP4 were also examined by applying conventional cut-offs to the standard DAS28-ESR4 (categorizing it into four disease activity levels) while applying Inoue et al. and Castrejón et al. cut-offs to DAS28-CRP4 (Standard, Hensor et al. and study-data-specific) (supplemental figures 4a and 4b). In contrast to the above results, agreements for the study-data-specific measures were lower than that for the standard and Hensor et al. measures. Highest agreement was observed for the standard DAS28-CRP4 (73%) using the Inoue cut-offs. For the study-data-specific DAS28-CRP4 measures (both unadjusted and adjusted for age-sex) simple agreement was

only 50% when Inoue et al cut-offs were applied and 66% with the Castrejón et al. cut-offs. With the Inoue et al cut-offs, simple kappa 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. cut-offs, the kappas 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 various cut-offs, Figure 3a) when the same cut-offs were applied to both DAS28-ESR4 and DAS28-CRP4. Mixed results were obtained for simple kappa.

DISCUSSION

In this analysis, we observed that even though DAS28-ESR and DAS28-CRP were highly positively correlated, DAS28-ESR was significantly higher than DAS28-CRP, both with and without patient's global assessment of disease activity being included 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, rheumatoid factor, anti-CCP antibody, and shared epitope. Though overall agreement and kappa (agreement above chance) were higher between DAS28-ESR4 and DAS28-CRP4 than that between DAS28-ESR3 and DAS28-CRP3, the values were low in general. As compared to the standard measures DAS28-CRP4, the study-data-specific measures (unadjusted/adjusted for age and sex) significantly improved agreement, including kappa, even with conventional cutoffs.

The strong positive correlation between DAS28-ESR and DAS28-CRP observed in this 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 only indicates that increase in one variable is also accompanied by increase in another variable. The differences between the two scores could be examined in two ways: a) as a continuous measure compare means/medians of DAS28-ESR and DAS28-CRP in the same participants, or b) examining the DAS28 categories (high, moderate, low and remission) and then comparing them with regard to agreement and kappa. 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 kappa were low. The finding of discrepant scores with DAS28-ESR being higher than DAS28-CRP is similar as observed in other studies;^{3, 23–26, 37, 46, 47}; in contrast Wells et al.²² found a high degree of agreement between the scores. Furthermore, in this study, the differences between DAS28-ESR and DAS28-CRP remained significant even when stratified by age, sex, disease duration, rheumatoid factor, 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, influence age and sex has also been evaluated in detail in other studies.^{35, 37}

In this study, DAS28-CRP3 'underestimated' disease activity in 47% participants and DAS28-CRP4 in 40% participants 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 months) were underestimated by DAS28-CRP4; also overall simple agreement (88.5%) and kappa (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 kappa=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 may be changed or new disease activity cutoffs could 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. In this analysis, we developed the study-data-specific definitions and examined how these and Hensor et al.³⁷ definitions (with and without age-sex adjustment) definitions would influence agreement between DAS28-ESR and DAS28-CRP. These agreements were examined using three cut-offs for disease activity: a) conventional, b) those suggested by Inoue et al.,²⁶ and c) 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 kappa 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 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, kappa, and underestimation by DAS28-CRP4. Also, the study-data-specific measures had higher agreement and kappa than that for the Hensor et al.³⁷ measures; to note the study-data-specific measures were constructed using the same strategy as that by Hensor et al., however, yielded different constants and multipliers for the DAS28-CRP4 formulae than that obtained in the Hensor et al. study.³⁷ Thus, even though Hensor et al. definitions improved agreement and kappa, using study-data-specific definitions might have 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 due to different population characteristics such as age, sex, race, disease duration to name a few; other studies^{22, 37} have also reported limitation in applying such cut-offs 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) cut-offs for the existing definitions. To further examine this, we examined agreement by applying conventional cut-offs (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) cut-offs 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 cut-offs. Whether a new definition and/or cut offs could increase external generalizability remains to be further examined.

Due to additional gain in agreement, Hensor et al.³⁷ have suggested use of age-sex adjusted definition for classifying patients into various DAS28 categories though not for EULAR 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 complexity of the formula and/or inability to have data on all the variables although age and sex of a patient are generally easily available and one can use a simple calculator or a nomogram or a computer (e.g. Microsoft Excel or a website). Though DAS28 has been shown to be useful in monitoring disease activity^{48–51} and is clinically interpretable⁴⁰ its usefulness in daily practice has been questioned.⁵² Therefore, we think a simple modification, without age-sex adjustment, in the conversion/multiplying factor with conventional cut-offs could be the optimal strategy to make the DAS28-ESR and DAS28-CRP equivalent.

One of the limitations of this study is relatively small sample size, especially while comparing DAS28-ESR4 vs. DAS28-CRP4 measures, and therefore, cross-validation of the modified formulae was not done. Small sample size was due to limited availability of ESR values on a subset of patients due to *CLEAR* registry protocol specifications. To note, however, that the primary aim of the study was not to develop new definitions per se but to examine agreement between the two measures. Although previous meta-analysis⁵³ has shown slight advantage of ESR for later time-points, CRP has been suggested to be a better measure to be used in multi-investigator studies due to its stability and ability to use frozen specimens by a central laboratory as performed in this study.⁵⁴

Although our sample size is smaller than that used for similar studies of RA patients 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 due to the fact that African-Americans are a minority group underrepresented in RA research,⁵⁵ we believe that our findings are of significant 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. And, therefore, we believe that inclusion of the excluded participants would not have changed the conclusions of the study, though certainly it would have added to the precision of the parameter estimates. However, the possibility of differences with regard to other unmeasured variables can not be ruled out. Although the general findings of this 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 which could be said to be shared by other studies.³⁷

In conclusion, despite there being a strong correlation, significant discrepancy between DAS28-ESR and DAS28-CRP exists which 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, whether population-specific definitions are needed or whether a ‘universal’ DAS28-CRP definition could be derived using variety of databases and/or whether different cutoffs for DAS28-ESR and DAS28-CRP are needed remains to be examined.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1a.

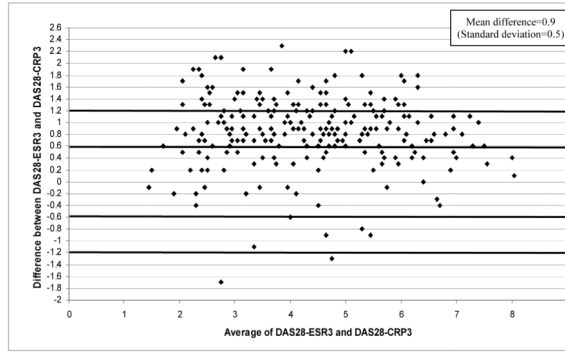


Figure 1b.

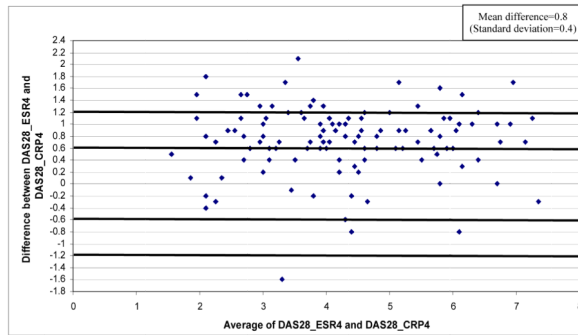


Figure 1.

Figure 1a. Bland-Altman plot analysis of DAS28-ESR3 vs. DAS28-CRP3, N=233

Figure 1b. Bland-Altman plot analysis of DAS28-ESR4 vs. DAS28-CRP4, N=120

Note: 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.

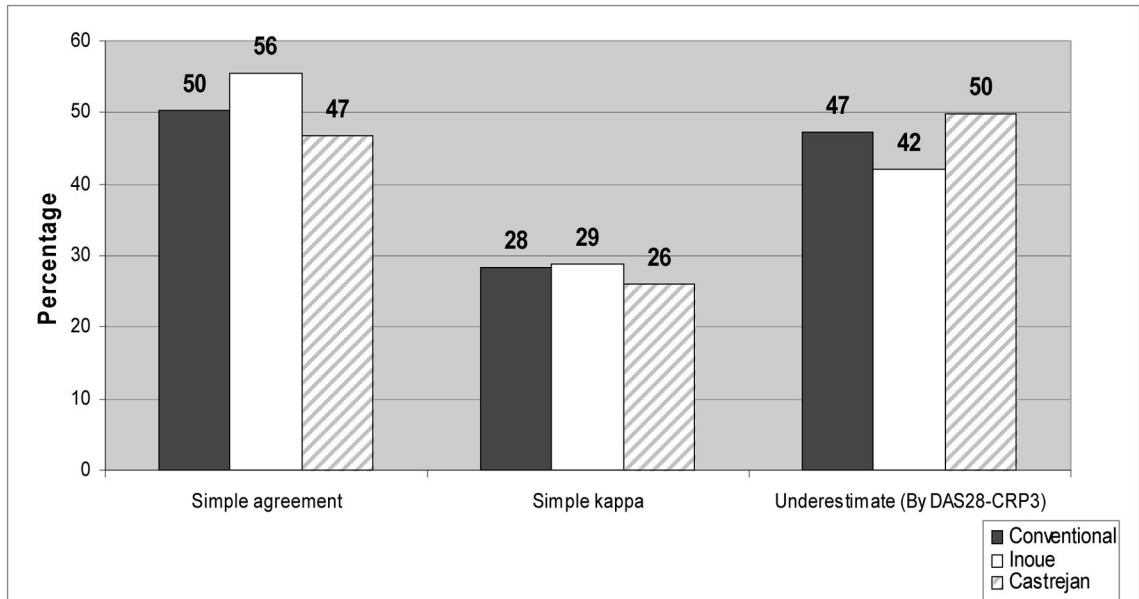


Figure 2. Agreement between the standard DAS28-ESR3 and the standard DAS28-CRP3 measures by various (conventional,^{39,40} Inoue et al.,²⁶ and Castrejan et al.²⁰) cut-off values for disease activity categories.

Note: Cut-offs: Conventional (5.1, 3.2, 2.6); Inoue et al. (4.1, 2.7, 2.3); Castrejan et al. (4.9, 3.8, 2.3).

Figure 3a.

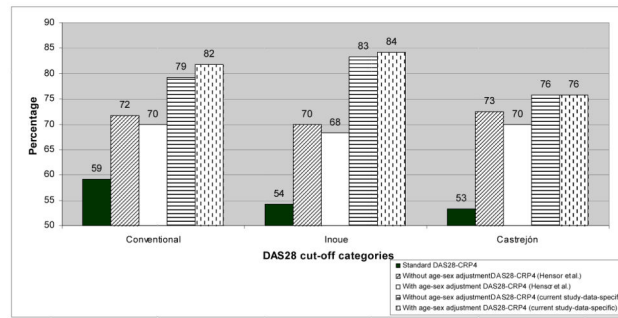


Figure 3b.

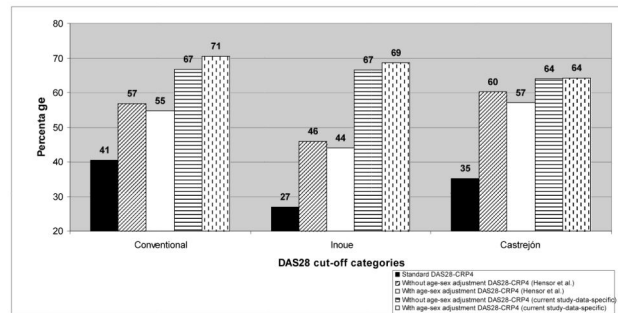


Figure 3c.

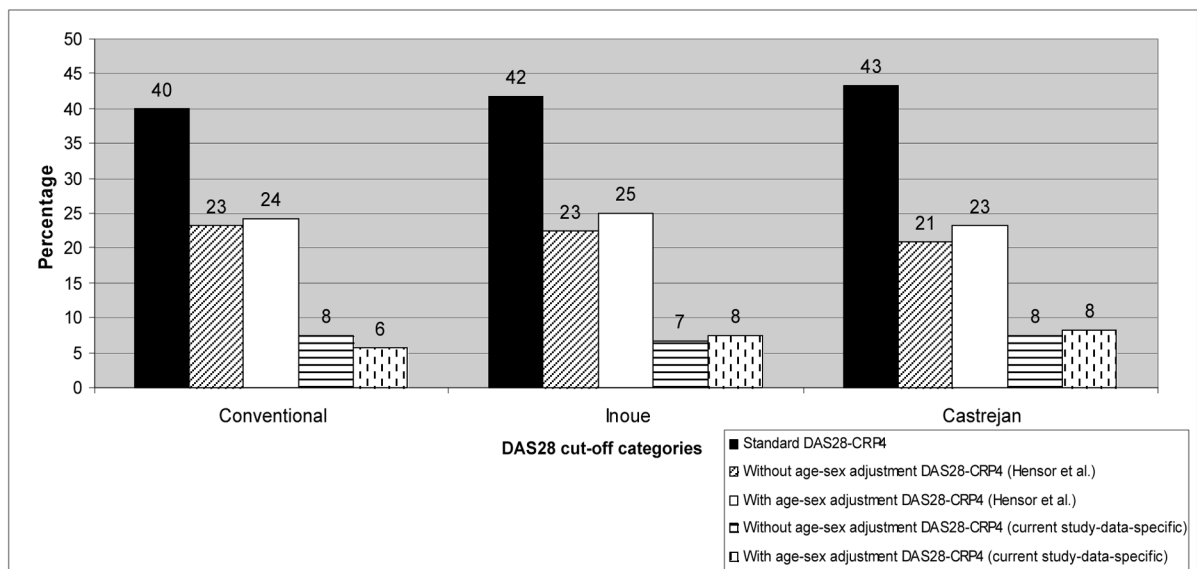


Figure 3. Figure 3a. Comparison of simple agreement between the standard DAS28-ESR4 and various DAS28-CRP4 measures by different cut-off values for disease-activity categories

Figure 3b. Comparison of simple kappa between the standard DAS-ESR4 and various DAS28-CRP4 measures by different cut-off values for disease-activity categories.

Note: Cut-offs: Conventional (5.1, 3.2, 2.6);^{39,40} Inoue et al. (4.1, 2.7, 2.3);²⁶ Castrejan et al. (4.9, 3.8, 2.3).²⁰

Figure 3c. Underestimation by DAS28-CRP4 relative to DAS28-ESR4 by different cut-off values for disease-activity categories

Note: Cut-offs: Conventional (5.1, 3.2, 2.6);^{39,40} Inoue et al. (4.1, 2.7, 2.3);²⁶ Castrejan et al. (4.9, 3.8, 2.3).²⁰

Table 1

Outcome measures used in the study

Outcome measures	Formula/Definition
A) Standard	
DAS28-ESR3	$(0.56 \cdot \sqrt{\text{Tender}} + 0.28 \cdot \sqrt{\text{Swollen}} + 0.70 \cdot \ln(\text{ESR})) \cdot 1.08 + 0.16$
DAS28-ESR4	$0.56 \cdot \sqrt{\text{Tender}} + 0.28 \cdot \sqrt{\text{Swollen}} + 0.70 \cdot \ln(\text{ESR}) + 0.014 \cdot (\text{VAS})$
DAS28-CRP3	$(0.56 \cdot \sqrt{\text{Tender}} + 0.28 \cdot \sqrt{\text{Swollen}} + 0.36 \cdot \ln(\text{CRP+1})) \cdot 1.10 + 1.15$
DAS28-CRP4	$0.56 \cdot \sqrt{\text{Tender}} + 0.28 \cdot \sqrt{\text{Swollen}} + 0.36 \cdot \ln(\text{CRP+1}) + 0.014 \cdot (\text{VAS}) + 0.96$
B) Hensor et al.³⁷	
Unadjusted ^a DAS28-CRP4	$0.56 \cdot \sqrt{\text{Tender}} + 0.28 \cdot \sqrt{\text{Swollen}} + 0.292 \cdot \ln(\text{CRP+1}) + 0.014 \cdot (\text{VAS}) + 1.523$
Adjusted ^b DAS28-CRP4	$0.56 \cdot \sqrt{\text{Tender}} + 0.28 \cdot \sqrt{\text{Swollen}} + 0.288 \cdot \ln(\text{CRP+1}) + 0.014 \cdot (\text{VAS}) + 0.003 \cdot (\text{Age}) + 0.159$ (if female) + 1.238
C) Current study-data-specific	
Unadjusted ^a DAS28-CRP4	$0.56 \cdot \sqrt{\text{Tender}} + 0.28 \cdot \sqrt{\text{Swollen}} + 0.1918 \cdot \ln(\text{CRP+1}) + 0.014 \cdot (\text{VAS}) + 2.086$
Adjusted ^b DAS28-CRP4	$0.56 \cdot \sqrt{\text{Tender}} + 0.28 \cdot \sqrt{\text{Swollen}} + 0.1878 \cdot \ln(\text{CRP+1}) + 0.014 \cdot (\text{VAS}) + 0.0073 \cdot (\text{Age}) + 0.2501$ (if female) + 1.49843

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's global assessment of disease activity on a visual analog scale of 0 to 100 mm.

^a Unadjusted for age and sex.

^b Adjusted for age and sex.

Table 2

Socio-demographic and clinical characteristics of the *CLEAR*^a participants for whom both DAS28-ESR and DAS28-CRP were available

Characteristic	N	Mean (SD)	Median (Q1 – Q3)
Age at enrollment, years	233	52.6 (12.4)	51.9 (45.5 – 59.0)
Age at RA onset, years	233	46.0 (13.7)	45.3 (37.3 – 53.7)
Disease duration at enrollment, years	233	6.6 (9.3)	1.8 (0.8 – 9.3)
ESR (mm/hr)	233	44.3 (27.8)	40 (22 – 61)
hsCRP (mg/l)	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), only <i>CLEAR II</i>	120	49.1 (27.0)	51 (28 – 68)
DAS28			
Using 3 variables: Tender, Swollen, ESR/CRP			
DAS28-ESR3 (both <i>CLEAR I and II</i>)	233	4.8 (1.5)	4.7 (3.7 – 5.9)
DAS28-CRP3 (both <i>CLEAR I and II</i>)	233	3.9 (1.5)	3.8 (2.7 – 5.1)
Paired t-test, p-value ^b		<0.001	-
Using 4 variables: Tender, Swollen, ESR/CRP, VAS			
DAS28-ESR4 (only <i>CLEAR II</i>)	120	4.7 (1.4)	4.6 (3.6 – 5.7)
DAS28-CRP4 (only <i>CLEAR II</i>)	120	3.9 (1.4)	3.9 (2.8 – 4.9)
Paired t-test, p-value ^b		<0.001	-

NOTE: DAS28 form and therefore VAS was not available for *CLEAR I* participants but only for *CLEAR II* participants.

SD=Standard deviation; Q1=First quartile; Q3=Third quartile; RA=Rheumatoid arthritis; ESR=Erythrocyte sedimentation rate by Westergreen method; CRP=High sensitivity C-reactive protein; DAS28=Disease activity score 28; HAQ=Health assessment questionnaire; VAS=Visual analog scale, self-assessed patient's global assessment of disease activity on a visual analog scale of 0 to 100 mm.

^a Consortium for the Longitudinal Evaluation of African Americans with Early Rheumatoid Arthritis (*CLEAR*) registry.

^b P-value for comparing means.

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 : >5.1	50	3	0	0	53
Moderate : ≥3.2 to ≤5.1	43	52	2	1	98
Low : ≥2.6 to <3.2	0	30	3	0	33
Remission: <2.6	0	20	17	12	49
DAS28-ESR4					
	N=43	N=57	N=11	N=9	N=120
DAS28-CRP4					
High : >5.1	27	0	0	0	27
Moderate : ≥3.2 to ≤5.1	16	35	0	1	52
Low : ≥2.6 to <3.2	0	14	1	0	15
Remission: <2.6	0	8	10	8	26

NOTE: High, moderate, low and remission are the disease activity categories with respective cut-offs shown.

- Self-assessed patient's 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 bold font indicate agreement between the two scores.

- Triangles include the number of patients for whom disease activity would be 'underestimated' if DAS28-CRP is used instead of DAS28-ESR.

DAS28=Disease activity score 28; ESR=Erythrocyte sedimentation rate by Westergreen method; CRP=C-reactive protein;