Clin Rheumatol (2014) 33:783–789
DOI 10.1007/s10067-014-2538-x

ORIGINAL ARTICLE

Interchangeability of 28-joint disease activity scores using the erythrocyte sedimentation rate or the C-reactive protein as inflammatory marker

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Received: 26 November 2013 / Revised: 24 January 2014 / Accepted: 10 February 2014 / Published online: 23 February 2014

Abstract This paper aims to examine the interchangeability of the disease activity score in 28 joints (DAS28)-erythrocyte sedimentation rate (ESR) and DAS28-CRP scores in a diverse sample of rheumatoid arthritis (RA) patients and to evaluate generalizability over gender, age, and disease duration. A sample of 682 patients was drawn from the DREAM registry. Agreement between the two DAS28 scores was analyzed using the intraclass correlation coefficient (ICC), Bland Altman plots, and a matrix of classification agreement over DAS28 disease activity categories. Despite a strong linear correlation between the DAS28 scores and a high ICC value of 0.931, a considerable lack of individual agreement could be observed, with Bland-Altman 95 % limits of agreement ranging between −0.85 and +1.25 points. On average, DAS28-CRP scores were 0.20 points lower than DAS28-ESR scores, and data stratification on age and gender showed that this systematic bias was most severe in older women (0.39 points). The overall classification agreement across DAS28 categories was 76.69 %, with the agreement being lowest (35.37 %) in the low disease activity group. Patients were more easily classified as being in remission when using the DAS28-CRP measure. DAS28-ESR and DAS28-CRP scores are not interchangeable within individuals. The DAS28-CRP tends to yield lower values of disease activity than the DAS28-ESR, resulting in substantial classification differences.

Keywords Agreement · DAS28-CRP · DAS28-ESR · Disease activity · Interchangeability · Rheumatoid arthritis

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Introduction

The disease activity score in 28 joints (DAS28) is a widely used outcome measure for assessing disease activity in rheumatoid arthritis (RA) patients [1]. It combines information on joint tenderness and joint swelling with a marker of inflammation and a patient-reported measure of general health. The DAS28 is not only widely used in clinical trials but is also often embedded within treatment protocols to monitor patients in daily clinical practice [2, 3]. Furthermore, its use is recommended by the European League Against Rheumatism (EULAR) [4].

Although the DAS28 was originally developed with the erythrocyte sedimentation rate (ESR) as inflammatory marker (i.e. the DAS28-ESR), it has since been suggested that C-reactive protein (CRP) may be used as an equivalent, which led to the development of a separate scoring algorithm of the DAS28, the DAS28-CRP [5]. However, several previous studies demonstrated lower disease activity scores and better responses in patients assessed with the DAS28-CRP instead of the DAS28-ESR [6–9], with a possible relationship to the patient's gender, age, and disease duration [6, 7, 10–14]. These score discrepancies might lead to different interpretations of a patient's level of disease activity and, consequently, to the undesirable situation that treatment decisions depend on the chosen DAS28 algorithm.

Table 1 Patient characteristics at baseline

Characteristic	Score range of measure	Mean (SD) or median (range)[a]
Gender (female)	–	428/682 (62.8 %)
Age (years)	–	57.69 (13.85)
Body mass index (kg/m^2)	–	26.47 (4.62)
Disease duration (years)	–	0 (0–51)
DAS28-ESR	0–10	3.88 (1.61)
DAS28-CRP	0–10	3.68 (1.45)
28-Tender joint count	0–28	2 (0–28)
28-Swollen joint count	0–28	3 (0–28)
Well-being	0–100	41.11 (26.60)
ESR (mm/h)	0–140	18 (1–120)
CRP (mg/l)	0–999	5 (1–158)
Pain	0–100	40.74 (26.81)
SF36—physical health	0–100	38.20 (9.37)
SF36—mental health	0–100	48.68 (11.46)
HAQ	0–3	0.88 (0–3)

[a] The values for gender are the number of patients/number of patients assessed

DAS-28 disease activity score for 28 joints, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *SF36* short form health survey with 36 items, *HAQ* health assessment questionnaire

This paper aims to examine the interchangeability of the DAS28-ESR and DAS28-CRP scores in a diverse sample of Dutch rheumatoid arthritis (RA) patients. Additionally, subanalyses will be performed to evaluate generalizability over gender, age, and disease duration.

Methods

Patients

The DREAM registry collects data in multiple centres and cohorts throughout the Netherlands while monitoring the disease of clinically diagnosed RA patients undergoing a variety of treatment strategies. Data was drawn from two different IRB approved studies within this registry, including all patients who had a valid measure of both the DAS28-ESR and the DAS28-CRP. This resulted in a heterogeneous group of males and females of various ages (all 18 years or older), with either early RA or longstanding RA. Informed consent was obtained from each patient.

Measures of disease activity

The DAS28 scores were calculated during each hospital visit using to the following formulas [4]:

1. $\mathrm{DAS28{-}ESR} = 0.56 \times \sqrt{\mathrm{TJC28}} + 0.28 \times \sqrt{\mathrm{SJC28}} + 0.70 \times \mathrm{Ln}(\mathrm{ESR}) + 0.014 \times \mathrm{GH}$
2. $\mathrm{DAS28{-}CRP} = 0.56 \times \sqrt{\mathrm{TJC28}} + 0.28 \times \sqrt{\mathrm{SJC28}} + 0.36 \times \mathrm{Ln}(\mathrm{CRP}+1) + 0.014 \times \mathrm{GH} + 0.96$

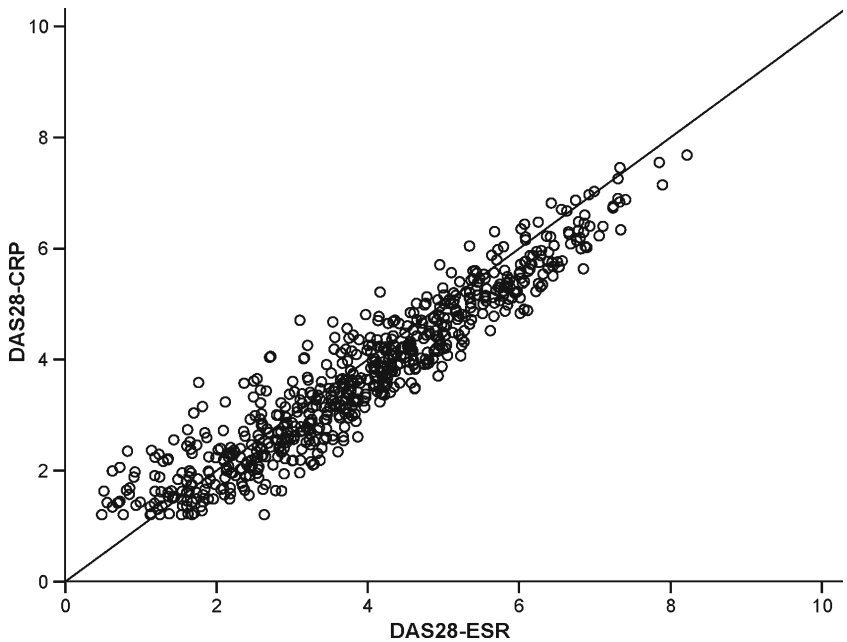


Fig. 1 The DAS28-ESR scores (*x*-axis) plotted against DAS28-CRP scores (*y*-axis). Each *point* corresponds to a single patient. The *solid line* indicates perfect agreement between the two DAS28-scores

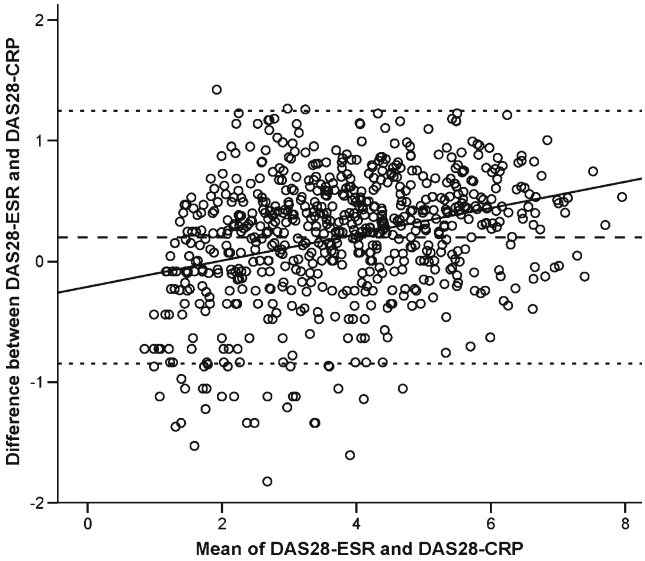


Fig. 2 Bland Altman plot of the DAS28-ESR and DAS28-CRP scores. The *dashed line* in the middle indicates the mean differences between both measures and the *upper* and *lower dotted lines* represent the 95 % limits of agreement. The *solid line* shows the regression line of the average difference

where the TJC28=tender joint count in 28 joints, SJC28=swollen joint count in 28 joints, and GH=a patient-reported visual analogue score of general health (on a scale of 0–100) [15]. CRP and ESR measures were determined on site, according to local standard practice.

Patients were classified into groups according to their current level of disease activity, i.e. remission if DAS28 <2.6, low disease activity if 2.6≤ DAS28 ≤3.2, moderate disease activity if 3.2< DAS28 ≤5.1, and high disease activity if DAS28 >5.1 [4].

Statistical analysis

Agreement between the DAS28-ESR and DAS28-CRP was first examined with a scatter plot and the two-way random, absolute agreement, single measures intraclass correlation coefficient (ICC). Next, Bland-Altman plots [16] were made to gain more insight into the size of individual differences over the total range of DAS28 scores. A Bland-Altman plot graphs the differences between the two DAS28 scores against their mean scores [16]. The plot reflects the average degree of bias (i.e. the mean difference), together with the 95 % limits of agreements (i.e. the mean score±1.96×standard deviation). Besides Bland-Altman analyses on the total patient sample, sub-analyses were performed based on disease duration (<1 vs. ≥1 year), age (<60 vs. ≥60 years), and gender. Finally, classification agreement of the DAS28-ESR and DAS28-CRP across DAS28 categories (i.e. remission/low/moderate/high disease activity) was determined, as well as category-specific agreement. All analyses were performed using SPSS version 21.0.

Results

Patient characteristics at baseline

Data was collected from a sample of 682 rheumatoid arthritis patients, predominantly female (62.8 %), with a mean age slightly below 60 years (57.69), and a mean disease duration of 1.51 years. Most patients did experience pain and swelling in their joints, had a diminished degree of well-being and physical functioning, and showed a moderately active disease with a DAS28-ESR score of 3.88 and a DAS28-CRP score of 3.68 (Table 1).

Agreement

Results showed a high ICC value of 0.931 and a strong, linear correlation between the DAS28-ESR and DAS28-CRP with a Pearson correlation coefficient of 0.945 (Fig. 1). Despite this high correlation, the Bland-Altman plot showed a considerable lack of agreement between the DAS-ESR and DAS-CRP, with 95 % limits of agreement ranging between −0.85 and +1.25 points (Fig. 2). On

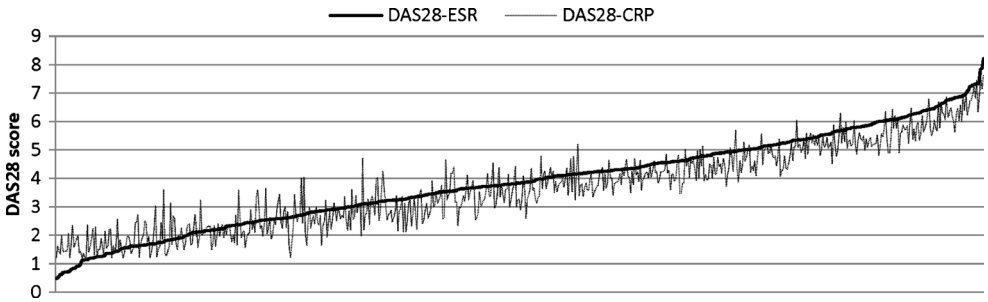
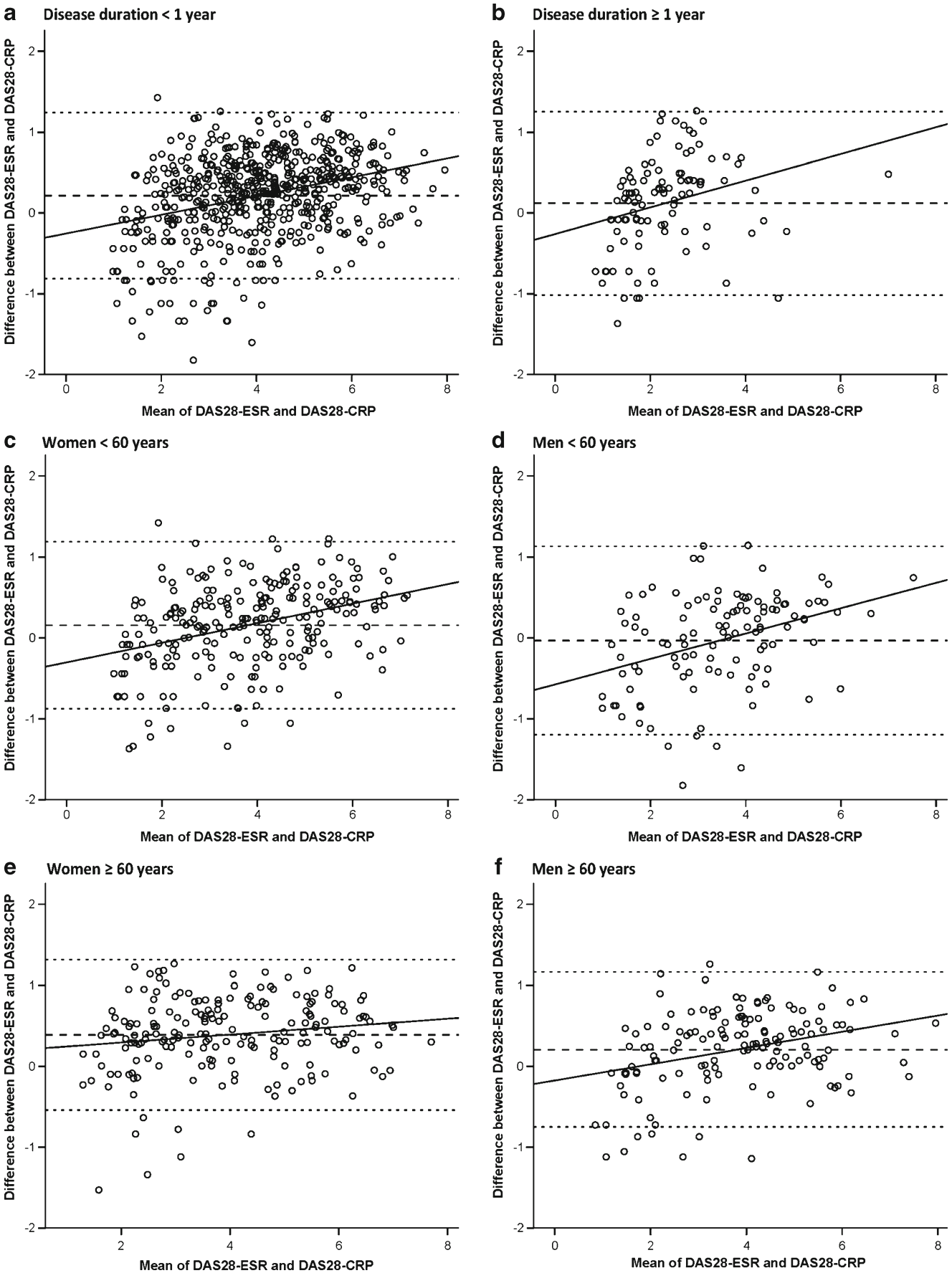


Fig. 3 Corresponding DAS28-CRP scores (*thin line*) to increasing DAS28-ESR scores (*thick line*)


a
Disease duration < 1 year
b
Disease duration ≥ 1 year
c
Women < 60 years
d
Men < 60 years
e
Women ≥ 60 years
f
Men ≥ 60 years
Difference between DAS28-ESR and DAS28-CRP
Mean of DAS28-ESR and DAS28-CRP

◀ **Fig. 4** Bland-Altman plot analyses of the DAS28-ESR and DAS28-CRP scores, divided into groups of different disease duration (**a** and **b**) and groups of different age and gender (**c–f**). Within each plot, the *dashed line* in the middle indicates the mean differences between both measures and the *upper* and *lower dotted lines* represent the 95 % limits of agreement. The *solid line* shows the regression line of the average difference

average, DAS28-CRP scores were 0.20 points lower than DAS28-ESR scores.

The amount of bias was dependent on the mean of the two DAS28 scores (r=0.31, p<0.01), with larger discrepancies for higher levels of disease activity (i.e. mean DAS28 values >4.0). Contrarily, for very low levels of disease activity, the DAS-ESR tended to yield lower values than the DAS-CRP (Fig. 3).

Sub-analyses on disease duration, age, and gender resulted in comparable Bland-Altman plots (Fig. 4). Bias was most pronounced in RA patients with a disease duration <1 year (0.21 points compared to 0.12 points in patients with a longer disease duration) and in older women (0.39 points vs. 0.16 for younger women, −0.03 for younger men, and 0.21 for older men).

Distribution disease activity groups

Overall, there was a 76.69 % classification agreement across DAS28 categories. In case of disagreement, the DAS28-CRP more often yielded a lower DAS28 classification than the DAS28-ESR (120 (75.47 %) vs. 39 (24.53 %) times, respectively). Category-specific agreement was generally high (>79 %), except for the low disease activity group, where it was only 35.37 %. Patients were more easily classified as being in remission when using the DAS28-CRP (Table 2).

Discussion

Despite the high correlation between both DAS28 scores and the *reasonably high* percentages of classification agreement over DAS28 categories, the DAS28-CRP tended to yield lower scores than the DAS28-ESR. These findings are consistent with previous studies [6–9] and emphasize the need for awareness of the score discrepancies between these two measures in order to improve standardization to make scores not only comparable within patients, but also between patients [7].

If the DAS28-CRP truly underestimates disease activity, this might preclude its use in treat-to-target strategies aimed at reaching sustained remission [8]. On the other hand, one might argue that the DAS28-ESR overestimates disease activity, whereby patients receive unnecessary medication if judgments are based solely on this score. Either way, the use of either one of these measures might lead to different interpretations of a patient's level of disease activity and, as a result, might lead to different treatment decisions. Nevertheless, one should keep in mind that the DAS28 scores are primarily statistical representations of a patient's disease activity and not necessarily clinical representations. They may serve as a guide but in clinical practice, rheumatologists may still observe disease activity while the DAS28 points towards a state of remission.

Category-specific agreement was especially poor within the low disease activity group. This is in accordance with the findings of Hensor et al. [9] and might (partly) be due to the lower number of patients in this category compared to the other categories; however, it does demonstrates the main area of concern when both DAS28 measures are assumed to be interchangeable. When using the DAS28-CRP, patients might too easily be categorized as being in remission.

Inconsistent instrument performances were also found over age, gender, and disease duration. Consistent with findings from Matsui et al. [6], the differences in the mean values between the DAS28-ESR and DAS28-CRP were larger for females than for males and increased with age. However, Matsui et al. [6] also found larger differences as disease duration increased, whereas we found that differences were largest in the RA group with disease duration <1year. This might be due to the composition of

Table 2 Comparison of disease activity according to the DAS28-ESR vs. DAS28-CRP

CRP ESR	Remission (DAS28 <2.6)	Low disease activity (2.6≤ DAS28 ≤3.2)	Moderate disease activity (3.2< DAS28 ≤5.1)	High disease activity (DAS28 >5.1)	Total
Remission	148 (21.70)	13 (1.91)	8 (1.17)	0 (−)	169 (24.78)
Low disease activity	31 (4.55)	26 (3.81)	13 (1.91)	0 (−)	70 (10.26)
Moderate disease activity	14 (2.05)	38 (5.57)	222 (32.55)	5 (0.73)	279 (40.91)
High disease activity	0 (−)	0 (−)	37 (5.43)	127 (18.62)	164 (24.05)
Total	193 (28.30)	77 (11.29)	280 (41.06)	132 (19.35)	682 (100)

The values correspond to the number of people in that category (%). A patient reaches remission if DAS28 <2.6, low disease activity if 2.6≤ DAS28 ≤3.2, moderate disease activity if 3.2< DAS28 ≤5.1, and high disease activity if DAS28 >5.1

ESR erythrocyte sedimentation rate, *CRP* C-reactive protein

our groups. By splitting the group at disease duration of 1 year, both groups will contain patients with relatively short disease duration. However, this low cut-off point of 1 year was chosen because of the large number of patients with a disease duration of less than 1 year (N=579) vs. patients with a disease duration ≥1 year (N=103). Consequently, effects of longer disease duration could not be adequately evaluated within this study.

Since the contribution of the tender joint count, swollen joint count, and general health measure are equal within the DAS28-ESR and DAS28-CRP (i.e. they have the same weighing in the algorithm), score deviations are completely attributable to differences in the ESR and CRP values. Although it is beyond the scope of this study to provide a discussion about which inflammatory marker to prefer as a marker of disease activity, it is recommended to look into this more thoroughly in future studies. Both of these markers are measuring slightly different aspects of the disease process [17]; it is assumed that ESR values tend to reflect the patient's disease activity over the past few weeks, whereas CRP values are a better reflection of short-term changes in disease activity [4–7, 17]. ESR values are believed to be affected by age and gender, whereas CRP values are not [6, 7, 10–13]. Underlying biological mechanisms might also explain (part of) these differences [13]. For instance, it has been shown that anaemia or abnormally shaped or sized red blood cells might influence ESR levels [18, 19]. Unfortunately, these effects could not be evaluated in this study because this kind of data was not available.

The score deviations cannot simply be solved by adding a constant to the DAS28-CRP (or by subtracting a constant from the DAS28-ESR), since score deviations were found to depend on the degree of disease activity. Therefore, if a rheumatologist wishes to use both scores interchangeably, future studies should focus on finding a robust way to handle the discrepancies in such a way that the transformation is generalizable across distinct patient groups. However, as pointed out by Wells et al. [7] this will not be easy. Specifying distinct disease activity thresholds for the DAS28-ESR and the DAS28-CRP might help in making them comparable. Another solution, as discussed by Hensor et al. [9], might be to incorporate age and gender as variables in the formula.

In conclusion, DAS28-ESR and DAS28-CRP scores are not interchangeable within individuals. The DAS28-CRP tends to yield lower values of disease activity than the DAS28-ESR, resulting in substantial classification differences.

Conflict of interest This is an unfunded study and the authors declare that they have no conflicts of interest.

Disclosures None.

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