Chapter 3

Calculating the ankylosing spondylitis disease activity score if the conventional C-reactive protein level is below the limit of detection or if high-sensitivity C-reactive protein is used: an analysis in the DESIR cohort

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ARTHRITIS RHEUMATOL. 2015 FEB;67(2):408-13

ABSTRACT

Objectives

The Ankylosing Spondylitis Disease Activity Score (ASDAS) is a composite measure of disease activity in axial spondyloarthritis. The aims of this study were to determine the most appropriate method for calculating the ASDAS using C-reactive protein (CRP) level when the conventional CRP level is below the limit of detection, to determine how low CRP values obtained by high-sensitivity CRP (hsCRP) measurement influence ASDAS-CRP results, and to test agreement between different ASDAS formulae.

Methods

Patients with axial spondyloarthritis who had a conventional CRP level below the limit of detection (5 mg/liter) were selected (n=257). The ASDAS-conventional CRP with 11 different imputations for the conventional CRP value (range 0-5 mg/liter, at 0.5 mg/liter intervals) was calculated. The ASDAS-hsCRP and ASDAS using the erythrocyte sedimentation rate (ESR) were also calculated. Agreement between ASDAS formulae was tested.

Results

The ASDAS-hsCRP showed better agreement with the ASDAS-CRP calculated using the conventional CRP imputation values of 1.5 and 2.0 mg/liter and with the ASDAS-ESR than with other imputed formulae. Disagreement occurred mainly in lower disease activity states (inactive/moderate disease activity). When the CRP value was <2 mg/liter, the resulting ASDAS-CRP scores may have been inappropriately low.

Conclusion

When the conventional CRP level is below the limit of detection or when the hsCRP level is <2mg/liter, the constant value of 2 mg/liter should be used to calculate the ASDAS-CRP score. There is good agreement between the ASDAS-hsCRP and ASDAS-ESR; however, formulae are not interchangeable.

INTRODUCTION

The Ankylosing Spondylitis Disease Activity Score (ASDAS) is a composite index to assess disease activity in axial spondyloarthritis (SpA).[1-3] It combines five single disease activity variables in such a manner that it optimally conveys information, resulting in one single score with better validity, enhanced discriminative capacity, and improved ability to detect change as compared to separate variables.[1-5] ASDAS cut-off values have been developed to define disease activity states and response criteria.[2]

The ASDAS has been endorsed by the Assessment of SpondyloArthritis international Society (ASAS) and by the Outcome Measures in Rheumatology study group and validated in various populations worldwide.[5-10] The ASAS membership has selected the ASDAS using the C-reactive protein (CRP) levels as the preferred version and the ASDAS using the erythrocyte sedimentation rate (ESR) as an alternative.[1-3] The same validated cut-off values apply to both the ASDAS-CRP and the ASDAS-ESR.[2]

The development and validation of the ASDAS was based on conventional CRP values. It has been suggested that when the conventional CRP is below the limit of detection and high-sensitivity CRP (hsCRP) is not available, 50% of the threshold value should be used to calculate the ASDAS-CRP.[2] However, this recommendation is not based on data-driven testing and the effect of using the hsCRP has not been determined. Further testing is required.

The aims of this study were to determine the best way to calculate the ASDAS when the conventional CRP is below the limit of detection, to study the influence of low CRP values obtained by hsCRP in the ASDAS-CRP, and to test agreement between different ASDAS formulae.

PATIENT AND METHODS

Patients

Baseline data from the Devenir des Spondylarthropathies Indifférenciées Récentes (DESIR) cohort was used. Details of the DESIR cohort have been previously described.[11] Briefly, DESIR is a French multicenter, prospective study of patients with early (<3 years´ duration) inflammatory back pain (IBP) suggestive of SpA. A total of 708 patients were included in the DESIR cohort at baseline. For the present study, we selected all patients who fulfilled the ASAS classification criteria for axial SpA[12] and who had a conventional CRP value below the limit of detection as well as the results of hsCRP testing; we used data from baseline assessments only. We used the dataset locked on 12 December 2011.

ASDAS Calculation

ASDAS-CRP and ASDAS-ESR scores were calculated based on 5 variables: acute-phase reactant levels (either CRP or ESR) and 4 patient-reported variables,[1,2] namely back pain (question 2 on the Bath Ankylosing Spondylitis Disease Activity Index [BASDAI][13]), duration of morning stiffness (question 6 on the BASDAI), peripheral pain/swelling (question 3 on the BASDAI), and patient global assessment of disease activity. All the patient-reported variables were scored on a scale of 0-10. ASDAS scores were also categorised according to previously published cut-off values for disease activity: an ASDAS score of <1.3 = inactive disease, ≥1.3-<2.1 = moderate activity, ≥2.1-3.5 = high activity, and >3.5 = very high disease activity.[2] Disease activity was quantified using the following equations:

ASDAS-CRP = (0.12*back pain) + (0.06*duration of morning stiffness) + (0.11*patient global) + (0.07*peripheral pain/swelling) + (0.58*ln[CRP +1])

or

ASDAS-ESR = (0.08*back pain) + (0.07*duration of morning stiffness) + (0.11*patient global) + (0.09*peripheral pain/swelling) + (0.29*√ESR)

The limit of detection by the conventional CRP assay was 5 mg/liter. The ASDAS-conventional CRP with 11 different imputations (from 0 mg/liter [ASDAS-CRP(0)] to 5 mg/liter [ASDAS-CRP(5)], at 0.5 mg/liter intervals) to replace the undetermined conventional CRP value was calculated. High-sensitivity CRP was measured by particle-enhanced immunoturbidimetry on a Cobas Integra 800 or Modular Analytics P800 device according to the instructions of the manufacturer (Roche Diagnostics). (Measurement was performed at Paris Bichat, a biologic resource center, by Dr. Joëlle Benessiano).

To gain insight into how low CRP values influence the total ASDAS-CRP score, we plotted CRP values against the CRP term 0.58*ln(CRP+1) from the ASDAS-CRP formula and displayed the ASDAS-CRP scores that were calculated using multiple CRP values (from 0 to 5 mg/liter) and different fixed values (from 0 to 5 units) for the 4 other variables included in the ASDAS-CRP formula (back pain, duration of morning stiffness, peripheral pain/swelling, and patient global assessment of disease activity).

Statistical analysis

The two-way mixed single-measures (absolute agreement) intraclass correlation coefficient (ICC) was used to assess agreement between the ASDAS-hsCRP and other ASDAS formulae (ASDAS-conventional CRP with different imputation strategies and ASDAS-ESR). The ICC can have values between 0 (no agreement) and 1 (perfect agreement).

Scatterplots were created to provide an additional view of the deviation of ASDAS-conventional CRP and ASDAS-ESR from ASDAS-hsCRP. Mean differences (and 95% confidence intervals) between ASDAS-hsCRP and other ASDAS formulae were also calculated.

Agreement between ASDAS-determined disease activity states was assessed using the kappa statistic. The kappa statistic represents the actual agreement beyond chance as a proportion of the potential agreement beyond chance. Since disease activity states are ordered categories, we used the weighted kappa value. The kappa statistic can have values between 0 (agreement equivalent to chance) and 1 (perfect agreement). The strenght of agreement was determined as follows: kappa values of <0.20 indicate poor agreement, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 good, 0.81-1.00 very good. SPSS version 22 and MedCalc version 13.1 were used in the statistical analyses.

RESULTS

Patient characteristics

A total of 260 patients fulfilled the inclusion criteria. Three patients had missing ASDAS results; therefore, data from 257 patients were available. Demographic and clinical characteristics of the study population are shown in supplementary table 1.

Agreement between ASDAS formulae

Table 1 shows the level of agreement between the results obtained using the different ASDAS formulae, both in terms of continuous variables (scores on the ASDAS) and in terms of the categorical variable (the disease activity state as determined by the score).

Quantitatively, the best agreement between the ASDAS-hsCRP and ASDAS-conventional CRP scores occurred with the imputed CRP values 1.0, 1.5, 2.0 and 2.5 mg/liter (ICC=0.94, 0.95, 0.94 and 0.92, respectively, representing very good agreement). Agreement between ASDAS-hsCRP and ASDAS-ESR was also very good (ICC=0.91) (table 1). As shown in the scatterplots presented in figure 1, use of conventional CRP imputation values ≤1.0 mg/liter systematically resulted in lower scores of the ASDAS-conventional CRP as compared to the ASDAS-hsCRP, while conventional CRP imputation values ≥2.5 mg/liter systematically resulted in higher scores on the ASDAS-conventional CRP compared to the ASDAS-hsCRP.

Table 1. Agreement between results obtained using the ASDAS-hsCRP and results obtained using other ASDAS formulae (ASDAS-conventional CRP with multiple imputation and ASDAS-ESR)*

	ASDAS-hsCRP vs. ASDAS calculated using other formulae (continuous variable)		ASDAS-hsCRP vs. ASDAS disease activity states calculated using other formulae (categorical variable)
	ICC (95% CI)	**Mean (95% CI) difference in ASDAS score**	**Weighted kappa (95% CI)**
ASDAS-CRP(0)	0.78 (-0.06 to 0.94)	-0.52 (-1.02 to -0.03)	0.51 (0.44 to 0.57)
ASDAS-CRP(0.5)	0.89 (0.33 to 0.96)	-0.29 (-0.79 to 0.21)	0.73 (0.67 to 0.79)
ASDAS-CRP(1)	0.94 (0.89 to 0.96)	-0.12 (-0.62 to 0.38)	0.73 (0.67 to 0.79)
ASDAS-CRP(1.5)	0.95 (0.93 to 0.96)	0.01 (-0.49 to 0.51)	0.75 (0.69 to 0.81)
ASDAS-CRP(2)	0.94 (0.90 to 0.96)	0.11 (-0.38 to 0.61)	0.76 (0.70 to 0.81)
ASDAS-CRP(2.5)	0.92 (0.70 to 0.96)	0.20 (-0.29 to 0.70)	0.71 (0.65 to 0.77)
ASDAS-CRP(3)	0.89 (0.37 to 0.96)	0.28 (-0.22 to 0.78)	0.66 (0.60 to 0.73)
ASDAS-CRP(3.5)	0.86 (0.11 to 0.96)	0.35 (-0.15 to 0.85)	0.64 (0.58 to 0.70)
ASDAS-CRP(4)	0.83 (0.00 to 0.95)	0.41 (-0.09 to 0.91)	0.61 (0.54 to 0.67)
ASDAS-CRP(4.5)	0.81 (-0.04 to 0.94)	0.47 (-0.03 to 0.96)	0.59 (0.53 to 0.65)
ASDAS-CRP(5)	0.78 (-0.06 to 0.94)	0.52 (0.02 to 1.01)	0.50 (0.44 to 0.57)
ASDAS-ESR	0.91 (0.85 to 0.94)	0.13 (-0.52 to 0.79)	0.69 (0.63 to 0.76)

*The Ankylosing Spondylitis Disease Activity Score (ASDAS) using the conventional C-reactive protein (CRP) level with 11 different imputations [ASDAS-CRP(0) to ASDAS-CRP(5), representing CRP values from 0 to 5 mg/liter, at 0.5 mg/liter intervals] and the ASDAS using the erythrocyte sedimentation rate (ESR) were calculated. Two hundred fifty-seven patients were used in all analyses except for the analyses of ASDAS-ESR (n= 246). hsCRP: high-sensitivity CRP; ICC: intraclass correlation coefficient; 95% CI: 95% confidence interval.

Qualitatively, the best agreement between ASDAS-hsCRP and ASDAS-conventional CRP disease activity states occurred with the conventional CRP imputation values of 1.5 and 2 mg/liter (weighted kappa=0.75 and 0.76, respectively, representing good agreement) (table 1). Agreement between ASDAS-hsCRP and ASDAS-ESR disease activity states was also good (weighted kappa=0.69). Disease activity states according to ASDAS-CRP(1.5) and ASDAS-CRP(2) had 78.2% and 78.1% agreement with ASDAS-hsCRP disease activity states, respectively. This percentage decreased to 53.3-75.6% when other CRP values were imputed. Disagreement was evident in lower disease activity states, namely shifts between inactive disease and moderate disease activity (supplementary table 2).

Effect of low CRP values on ASDAS-CRP scores

The values corresponding to y=0.58*ln(CRP+1), the CRP term from the ASDAS-CRP formula, according to CRP values between 0 and 5 mg/liter, were calculated. The function approximates y=0 asymptotically. For higher values, the relationship between

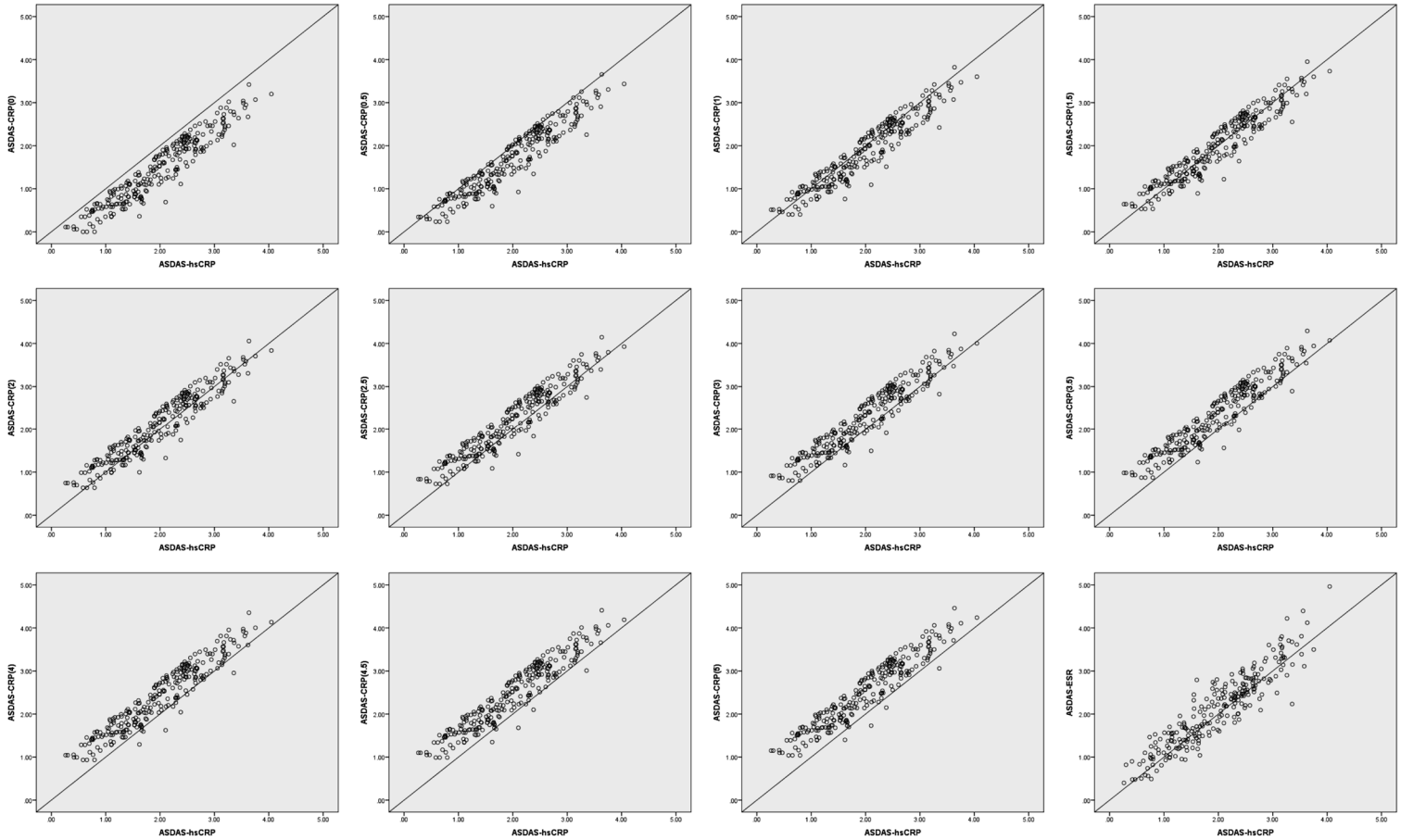

Figure 1. Scatterplots showing the relationship between the Ankylosing Spondylitis Activity Score (ASDAS) using high-sensitivity C-reactive protein (hsCRP) measurement and other ASDAS formulae (ASDAS-conventional CRP [ASDAS-CRP] with multiple imputation of CRP values [ranging from 0 to 5 mg/liter, at 0.5 mg/liter intervals] and ASDAS using the erythrocyte sedimentation rate [ESR]). The line indicates exact agreement between the ASDAS formulae. Data on 257 patients were used for all analyses except for analysis on the relationship between ASDAS-hsCRP and ASDAS-ESR, where data on 246 patients were used.

CRP and 0.58*ln(CRP+1) is roughly linear. However, for lower values, small differences in the CRP value represent larger steps in the term 0.58*ln(CRP+1) because the steepness of the curve increases in this area, which may result in inappropriately low ASDAS scores. This implies that it may be better not to use very low CRP values when calculating the ASDAS-CRP. The decision about the optimal CRP threshold value can be made by examining hypothetical case scenarios. A graphic representation of the results of this analysis, illustrating that this threshold should be between 1.5 and 2.5 mg/liter, is presented in supplementary figure 1.

Table 2 is a matrix showing ASDAS-CRP scores for hypothetical scenarios in which different CRP values and different fixed values for the other 4 items used in the ASDAS-CRP formula were imputed. The 1.5, 2.0 and 2.5 mg/liter imputation strategies perform well with very subtle differences. However, looking at individual cases is particularly informative. If all the other variables are equal to 4, disease activity is rated as moderate when a CRP constant value of 1.5 is used (ASDAS 2.0) but high when a CRP constant value of 2 is used (ASDAS 2.1). Clinically, the latter scenario makes more sense. Further, if all the other variables are equal to 1.5, disease activity is rated as moderate when a constant value of 2.5 is used (ASDAS 1.3) but inactive when a CRP constant value of 2 is used (ASDAS=1.2). Again, clinically the latter scenario makes more sense. These two examples favour the use of the constant value of 2 mg/liter rather than 1.5 or 2.5 mg/liter as the ideal imputation strategy for very low CRP levels.

Table 2. ASDAS-conventional CRP results for different CRP values and different fixed values for all the other four variables used in the calculation of the ASDAS-CRP formula

CRP (mg/liter)	ASDAS-CRP									
	All other variables=0	All other variables=1	All other variables=1.5	All other variables=2	All other variables=2.5	All other variables=3	All other variables=3.5	All other variables=4	All other variables=4.5	All other variables=5
0	0.0	0.4	0.5	0.7	0.9	1.1	1.3	1.4	1.6	1.8
0.5	0.2	0.6	0.8	1.0	1.1	1.3	1.5	1.7	1.9	2.0
1	0.4	0.8	0.9	1.1	1.3	1.5	1.7	1.8	2.0	2.2
1.5	0.5	0.9	1.1	1.3	1.4	1.6	1.8	2.0	2.2	2.3
2	0.6	1.0	1.2	1.4	1.5	1.7	1.9	2.1	2.3	2.4
2.5	0.7	1.1	1.3	1.4	1.6	1.8	2.0	2.2	2.3	2.5
3	0.8	1.2	1.3	1.5	1.7	1.9	2.1	2.2	2.4	2.6
3.5	0.9	1.2	1.4	1.6	1.8	2.0	2.1	2.3	2.5	2.7
4	0.9	1.3	1.5	1.7	1.8	2.0	2.2	2.4	2.6	2.7
4.5	1.0	1.3	1.5	1.7	1.9	2.1	2.2	2.4	2.6	2.8
5	1.0	1.4	1.6	1.8	1.9	2.1	2.3	2.5	2.7	2.8

*The Ankylosing Spondylitis Disease Activity Score (ASDAS) using the conventional C-reactive protein (CRP) level was calculated using multiple CRP values (ranging from 0 to 5 mg/liter, at 0.5 mg/liter intervals) and multiple fixed values (from 0 to 5 units, at 0.5-unit intervals) for the other 4 variables used in the calculation of the ASDAS-CRP (back pain, duration of morning stiffness, peripheral pain/swelling, and patient global assessment of disease activity). ASDAS scores were categorized as follows: <1.3 = inactive disease (lightly shaded), ≥1.3-<2.1 = moderate disease activity (shaded), ≥2.1-3.5 = high activity (darkly shaded), and >3.5 = very high disease activity.

DISCUSSION

The availability of conventional CRP and hsCRP determinations in the DESIR cohort allowed us to perform this analysis in a large population of patients with early IBP who fulfilled the ASAS classification criteria for axial SpA. Our study shows that when the conventional CRP value is below the limit of detection, the value of 2 mg/liter should be used to calculate the ASDAS-CRP. Furthermore, when the hsCRP value is below 2 mg/L, the constant value of 2 mg/liter should also be used to calculate the ASDAS-CRP.

We have shown that for very low hsCRP values, small differences represent larger steps in the CRP term of the ASDAS formula and therefore larger steps in the total ASDAS-CRP score. The final choice of the best imputation value was made by looking at a matrix of clinical scenarios (table 2) according to different imputation strategies. Differences between the imputation of the 1.5, 2.0 and 2.5 mg/liter CRP values were small, but the analysis of individual cases regarding the repercussion of these different imputation strategies in ASDAS disease activity states allowed us to conclude that the best option was not to use hsCRP values below 2 mg/liter.

Disagreement between the ASDAS-hsCRP and other ASDAS formulae was mainly evident among lower disease activity states (inactive/moderate disease activity), a shift that has fewer therapeutic implications than the shift between moderate and high/very high disease activity. This is particularly important given recent evidence that the ASDAS cut-off for high disease activity (ASDAS ≥2.1) is likely to be the most appropriate ASDAS cut-off value for use in the selection of patients for tumor necrosis factor blocker treatment.[14,15] Further evidence supports the replacement of the commonly used BASDAI selection cut-off of 4 units (on a 0-10 scale) by the ASDAS high disease activity cut-off.[16] There was also a high level of agreement between the ASDAS-hsCRP and ASDAS-ESR. However, it is important to highlight that formulae are not interchangeable.

One of the limitations of our study is the fact that this is a selected population with early disease. Therefore results might not be generalisable to the entire spectrum of axial SpA patients, in particular to patients with advanced disease/ankylosing spondylitis. However, a lack of generalisability is unlikely given the fact that CRP is more frequently elevated in ankylosing spondylitis than in non-radiographic axial SpA, so the need to substitute conventional CRP values below the limit of detection or very low hsCRP values will occur more often in early disease than in late disease.[17]

The ASDAS is increasingly being used as a measure of disease activity in clinical practice, clinical trials and observational studies[16]. This study contributes to further standardisation of the ASDAS and to a more homogeneous and reproducible application of this new index.

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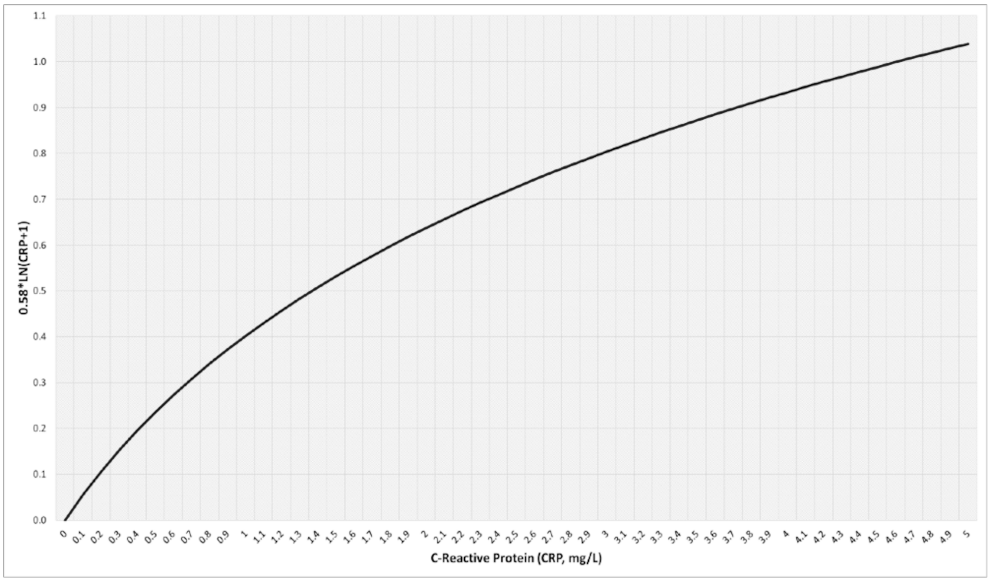
SUPPLEMENTARY MATERIAL

Supplementary table 1. Summary of the baseline clinical and demographic characteristics of the study population (n=257)*

Male, no (%)	121 (47.1)
Caucasian, no (%)	234 (91.1)
Age, years	33.2 (8.8)
HLA-B27 positive, no (%)	191 (89.7)
ASDAS-hsCRP	2.0 (0.8)
ASDAS-ESR[a]	2.2 (0.9)
hsCRP, mg/liter	1.7 (1.4)
ESR†, mmHg	8.2 (6.9)
BASDAI (0-10 scale)	4.0 (2.1)
Patient global assessment (0-10 scale)	4.6 (2.7)
Physician global assessment (0-10 scale)	3.9 (2.2)
BASMI (0-10 scale)	2.2 (0.9)
BASFI (0-10 scale)	2.6 (2.2)

*Except were indicated otherwise, values are the mean (standard deviation). [a]ESR was not available in 4.3% (11/257) of the patients. ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; BASFI: Bath Ankylosing Spondylitis Functional Index; CRP: C-reactive protein; hsCRP: high sensitivity CRP; ESR: erythrocyte sedimentation rate.



Supplementary figure 1. Graphic displaying the results of the C-reactive protein (CRP) component of the ASDAS-CRP formula (0.58*ln(CRP+1)) according to the CRP value, from 0 to 5 mg/liter, at 0.1 mg/liter intervals.

Supplementary table 2. Percentage and causes of disagreement in ASDAS disease activity states using ASDAS-hsCRP and other ASDAS formulae (ASDAS-conventional CRP with multiple imputation strategies* and ASDAS-ESR)

ASDAS formulae	ASDAS-hsCRP
	ASDAS disease activity states, percentage and causes of disagreement
ASDAS-CRP(0)	**Disagreement: 46.7%** MDA → ID: 21.0%; HDA → ID: 2%; HDA → MDA: 20.6%; VHDA → HAD: 3.1%
ASDAS-CRP(0.5)	**Disagreement: 25.0%** ID → MDA: 0.4%; MDA → ID: 12.5%; MDA → HAD: 0.4%; HDA → MDA: 8.6%; HAD → ID: 0.4%; VHDA → HAD: 2.7%
ASDAS-CRP(1)	**Disagreement: 24.4%** ID → MDA: 3.1%; MDA → ID: 10.1%; MDA → HAD: 2.3%; HDA → MDA: 6.2%; HAD → ID: 0.4%; VHDA → HAD: 2.3%
ASDAS-CRP(1.5)	**Disagreement: 21.9%** ID → MDA: 5.1%; MDA → ID: 5.4%; MDA → HAD: 4.7%; HDA → MDA: 4.7%; HAD → ID: 0.4%; HDA → VHDA: 0.4%; VHDA → HAD: 1.2%
ASDAS-CRP(2)	**Disagreement: 21.8%** ID → MDA: 6.6%; MDA → ID: 2.7%; MDA → HAD: 6.6%; HDA → MDA: 4.3%; HDA → VHDA: 1.2%; VHDA → HAD: 0.4%
ASDAS-CRP(2.5)	**Disagreement: 25.3%** ID → MDA: 10.9%; MDA → ID: 1.6%; MDA → HAD: 8.2%; HDA → MDA: 2.3%; HDA → VHDA: 1.9%; VHDA → HAD: 0.4%
ASDAS-CRP(3)	**Disagreement: 29.1%** ID → MDA: 13.2%; MDA → ID: 0.4%; MDA → HAD: 10.1%; HDA → MDA: 1.9%; HDA → VHDA: 3.1%; VHDA → HAD: 0.4%
ASDAS-CRP(3.5)	**Disagreement: 31.6%** ID → MDA: 14.8%; MDA → ID: 0.4%; MDA → HAD: 11.3%; HDA → MDA: 0.8%; HDA → VHDA: 4.3%
ASDAS-CRP(4)	**Disagreement: 34.3%** ID → MDA: 15.6%; MDA → ID: 0.4%; MDA → HAD: 13.2%; HDA → MDA: 0.8%; HDA → VHDA: 4.3%
ASDAS-CRP(4.5)	**Disagreement: 35.8%** ID → MDA: 17.5%; MDA → HAD: 10.1%; HDA → MDA: 2%; HDA → VHDA: 6.2%
ASDAS-CRP(5)	**Disagreement: 43.6%** ID → MDA: 17.9%; MDA → HAD: 18.7%; HDA → MDA: 0.4%; HDA → VHDA: 6.6%
ASDAS-ESR	**Disagreement: 28.1%** ID → MDA: 7.7%; MDA → ID: 3.3%; MDA → HAD: 8.5%; HDA → MDA: 3.3%; HDA → VHDA: 4.1%; VHDA → HAD: 1.2%

*ASDAS-CRP(0) to ASDAS-CRP(5) represents the ASDAS-CRP results with 11 imputation strategies for the conventional CRP, from 0 to 5 mg/liter, at 0.5 mg/liter intervals. ASDAS: Ankylosing Spondylitis Disease Activity Score; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; hsCRP: high sensitivity CRP; ID: inactive disease; MDA: moderate disease activity; HAD: high disease activity; VHDA: very high disease activity. Data on 257 patients were used for all analyses except for the ASDAS-ESR, where data on 246 patients were used.