

Running head: Improving and standardizing the calculation of the ASDAS

Title: How to calculate the ASDAS if the conventional CRP is below the limit of detection or if using high sensitivity CRP? – An analysis in the DESIR cohort

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Abstract

Background: The Ankylosing Spondylitis Disease Activity Score (ASDAS) is a composite measure of disease activity in axial spondyloarthritis.

Objectives: Our aims were to investigate the most appropriate ASDAS-C-reactive protein (ASDAS-CRP) calculation method when the conventional CRP (cCRP) is below the limit of detection, to study the arithmetic influence of low CRP values obtained by high sensitivity CRP (hsCRP) in ASDAS-CRP results and to test agreement between different ASDAS formulae.

Methods: Patients with axial spondyloarthritis and cCRP below the limit of detection (5mg/L, n=257) were selected. ASDAS-cCRP was calculated using eleven imputation strategies for the cCRP (range 0-5, at 0.5 intervals). ASDAS-hsCRP and ASDAS-ESR were also calculated. Agreement between ASDAS formulae was tested.

Results: ASDAS-CRP calculated with the cCRP imputation values of 1.5 and 2.0mg/L and ASDAS-erythrocyte sedimentation rate (ESR) had better agreement with ASDAS-hsCRP than other imputed formulae. Disagreement was mainly in lower disease activity states (inactive/moderate disease activity). When the CRP value is <2mg/L, the CRP component of the ASDAS-CRP formula can take very low values that may result in inappropriately low ASDAS-CRP values.

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

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 truth (validity), enhanced discriminative capacity and improved ability to detect change as compared to separate variables.[1-5] ASDAS cut-offs have been developed to define disease activity states and response criteria to treatment.[2]

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

The development and validation of the ASDAS was based on values with conventional CRP (cCRP). It was suggested that when the cCRP is below the limit of detection, and high sensitivity CRP (hsCRP) is not available, 50% of the threshold value should be used to calculate ASDAS-CRP.[2] However, neither this recommendation nor the effect of using hsCRP was data driven and requires further testing.

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

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 prospective, multicenter study of patients with early (<3 years) inflammatory back pain (IBP) suggestive of SpA. A total of 708 patients were included in the DESIR cohort at baseline. For this study, we selected all patients fulfilling the ASAS classification criteria for axial SpA with a cCRP value below the limit of detection and available hsCRP, and we have used baseline assessments only. We used the dataset locked on December 12th, 2011.

ASDAS Calculation

ASDAS-CRP and ASDAS-ESR were calculated based on 5 variables, one of the them being an acute phase reactant (either CRP or ESR) and the other four being patient-reported items,[1, 2] namely back pain (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] question 2), duration of morning stiffness (BASDAI question 6), peripheral pain/swelling (BASDAI question 3) and patient global assessment of disease activity. All the patient-reported variables were captured on a 0-10 numerical rating scale. ASDAS values were also categorised according to previously published cut-offs for disease activity states: inactive disease (ASDAS<1.3), moderate ($1.3 \leq \text{ASDAS} < 2.1$), high ($2.1 \leq \text{ASDAS} \leq 3.5$) and very high disease activity (ASDAS>3.5).[2]

The ASDAS formulae are presented below:

- a) $\text{ASDAS-CRP} = 0.12 \times \text{Back Pain} + 0.06 \times \text{Duration of Morning Stiffness} + 0.11 \times \text{Patient Global} + 0.07 \times \text{Peripheral Pain/Swelling} + 0.58 \times \text{LN}(\text{CRP (mg/L)} + 1)$
- b) $\text{ASDAS-ESR} = 0.08 \times \text{Back Pain} + 0.07 \times \text{Duration of Morning Stiffness} + 0.11 \times \text{Patient Global} + 0.09 \times \text{Peripheral Pain/Swelling} + 0.29 \times \sqrt{\text{ESR (mm/h)}}$

The limit of detection of the cCRP assay was 5 mg/L. ASDAS-cCRP was calculated using eleven different imputation strategies to replace the undetermined cCRP value, from 0mg/L (ASDAS-CRP(0)) to 5mg/L (ASDAS-CRP(5)), at 0.5mg/L intervals. hsCRP was measured by particle-enhanced immunoturbidimetry on a Cobas Integra 800 or ModularAnalytics P800 device (Roche Diagnostic System, Basel, Switzerland) according to the manufacturer's specifications in a biological resources centre (Paris Bichat, Joëlle Benessiano).

To gain insight into the influence of low CRP values in the total ASDAS-CRP result, we plotted CRP values against the CRP term ($0.58 \times \text{LN}(\text{CRP} + 1)$) of the ASDAS-CRP formula and created a table displaying ASDAS-CRP results for different CRP values (from 0 to 5mg/L) and different fixed values (from 0 to 5 units) for all the other items of the ASDAS-CRP formula.

Statistical analysis

The 2-way mixed model, absolute agreement type, single measures intraclass correlation coefficient (ICC) was used to assess agreement between ASDAS-hsCRP and other ASDAS formulae (ASAS-cCRP with different imputation strategies and ASDAS-ESR). The ICC can have values between 0 (no agreement at all) and 1 (perfect agreement).

Scatter plots were created to provide an additional view of the deviation of ASDAS-cCRP and ASDAS-ESR from ASDAS-hsCRP. Mean differences (and 95% confidence intervals) between ASDAS-hsCRP and others ASDAS formulae were also calculated.

Agreement between ASDAS disease activity states was assessed using the kappa statistics. 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. The kappa coefficient can have values between 0 (no agreement better than chance) and 1 (perfect agreement).

The strenght of agreement was interpreted as follows: <0.20, poor; 0.21-0.40, fair; 0.41-0.60, moderate; 0.61-0.80, good; 0.81-1.00, very good. SPSS v22 and MedCalc v13.1 were used in the statistical analyses.

RESULTS

Patients' characteristics

A total of 260 patients fulfilled the inclusion criteria. Three patients had missing ASDAS and therefore data from 257 patients was available. Supplementary table 1 shows the demographic and clinical characteristics of the study population.

Agreement between ASDAS formulae

Table 1 shows the level of agreement between ASDAS formulae, both as a continuous and as a categorical (disease activity states) variable.

Quantitatively, agreement between ASDAS-hsCRP and ASDAS-cCRP with the imputed values of 1.0, 1.5, 2.0 and 2.5mg/L was best and very similar (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).

Scatter plots (figure 1) showed that cCRP imputation values ≤ 1.0 mg/L resulted in systematically lower values of ASDAS-cCRP compared to ASDAS-hsCRP while cCRP imputation values ≥ 2.5 mg/L resulted in systematically higher values of ASDAS-cCRP compared to ASDAS-hsCRP.

Qualitatively, agreement between ASDAS-hsCRP and ASDAS-cCRP disease activity states was best with the cCRP imputation values of 1.5 and 2mg/L (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% with other imputation strategies. Disagreement was mainly in lower disease activity states, namely shifts between inactive disease and moderate disease activity (supplementary table 2).

Effect of low CRP values in ASDAS-CRP results

Supplementary figure 1 is the graphic representation of $y=0.58*\ln(\text{CRP}+1)$, the “CRP term” of the ASDAS-CRP formula, for CRP values between 0 and 5mg/L. The function approximates $y=0$ asymptotically. For higher values the relationship between CRP and $0.58*\ln(\text{CRP}+1)$ is roughly linear. However, for lower values, small differences in the CRP

value represent larger steps in the term $0.58 \cdot \ln(\text{CRP}+1)$ because the steepness of the curve increases in this area, which may result in inappropriately low ASDAS values. This implies that it may be better not to allow the CRP value to be too low when calculating ASDAS-CRP. The decision about the optimal CRP threshold value can be done by looking at hypothetical case scenarios (graphically it can already be seen that this threshold should be between 1.5 and 2.5 mg/L).

Table 2 is a matrix with ASDAS-CRP results for hypothetical scenarios with different CRP values and different fixed values for all the other four items of the ASDAS-CRP formula. The 1.5, 2.0 and 2.5mg/L imputation strategies perform well with very subtle differences. However, looking at individual cases is particularly informative; for example:

- a) if all the other variables are equal to 4, disease activity is moderate using the CRP constant value of 1.5 (ASDAS=2.0) but high using the CRP constant value of 2 (ASDAS=2.1): clinically the last scenario makes more sense;
- b) if all the other variables are equal to 1.5, disease activity is moderate (ASDAS=1.3) using the CRP constant value of 2.5 but inactive disease (ASDAS=1.2) using the CRP constant value of 2: again, clinically the last scenario makes more sense.

These two examples favour the use of the constant value of 2mg/L rather than 1.5 or 2.5mg/L as the ideal imputation strategy for very low CRP.

DISCUSSION

The availability of cCRP and hsCRP determinations in the DESIR cohort allowed us to perform this analysis in a large population of patients with early IBP fulfilling the ASAS classification criteria for axial SpA. Our study shows that when the cCRP value is below the limit of detection, the value of 2mg/L should be used to calculate ASDAS-CRP. Furthermore, when the hsCRP value is below 2mg/L, the constant value of 2mg/L should also be used to calculate 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 value. 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 2.5mg/L 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 2mg/dl.

Disagreement between ASDAS-hsCRP and other ASDAS formulae was mainly in lower disease activity states (inactive disease/moderate disease activity), a shift that has less 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 \geq 2.1) is likely to be the most appropriate ASDAS cut-off to select patients for TNF-blocker treatment, including accumulated evidence supporting the replacement of the commonly used BASDAI selection cut-off of 4 units (0-10 scale) by the ASDAS high disease activity cut-off.[12-14] There was also a high level of agreement

between 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 generalizable to the entire spectrum of axial SpA patients, in particular to patients with advanced disease/ankylosing spondylitis. However, the lack of generalizability is unlikely given by the fact that CRP is more frequently elevated in AS than in non-radiographic axial SpA, so the need to substitute cCRP values below the limit of detection or very low hsCRP values will occur more often in early disease than in late disease.[15]

ASDAS is increasingly being used as a measure of disease activity in clinical practice, clinical trials and observational studies.[14] This study contributes to further standardization of the ASDAS and to a more homogeneous and reproducible application of this new index.

Contributors: PM performed the statistical analysis and drafted the first version of the manuscript. All authors participated in the design of the study, interpreted the results and contributed to drafting the final version of the manuscript. All authors read and approved the final manuscript.

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Table 1 Agreement between ASDAS-hsCRP and other ASDAS formulae (ASDAS-cCRP with multiple imputation strategies* and ASDAS-ESR)

ASDAS formulae	ASDAS-hsCRP		
	ASDAS values		ASDAS disease activity states
	ICC (95% CI)	Mean difference (95% CI)	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)

*ASDAS-CRP(0) to ASDAS-CRP(5) represents the ASDAS-CRP results with eleven imputation strategies for the conventional CRP, from 0 to 5mg/L, at 0.5mg/L intervals. ASDAS, Ankylosing Spondylitis Disease Activity Score; CRP, C-reactive protein; CI, confidence interval; ESR, erythrocyte sedimentation rate; ICC, intraclass correlation coefficient; hs, high sensitivity. The total number of patients is 257, except for the ASDAS-ESR analysis where the total number of patients is 246.

Table 2 ASDAS-CRP results for different CRP values (from 0 to 5mg/L, at 0.5mg intervals) and different fixed values (from 0 to 5 units, at 0.5 units intervals) for all the other four items in the ASDAS-CRP formula

CRP (mg/L)	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

ASDAS, Ankylosing Spondylitis Disease Activity Score; CRP, C-reactive protein. All values are rounded to one decimal place. Light grey, inactive disease; grey, moderate disease activity; dark grey, high disease activity.

Figure 1 ASDAS-hsCRP plotted against other ASDAS formulae (ASDAS-cCRP with different imputation strategies and ASDAS-ESR). The diagonal line indicates exact agreement between the ASDAS formulae; total n=257, except for the ASDAS-ESR scatter plot where n=246.

Supplementary figure 1 Graphic displaying the results of the CRP component of the ASDAS-CRP formula ($0.58 \cdot \ln(\text{CRP}+1)$) according to the CRP value, from 0 to 5mg/L, at 0.1 mg/L intervals.

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