Gender stratified adjustment of the DAS28-CRP improves inter-score agreement with the DAS28-ESR in rheumatoid arthritis

Authors:

Philip D. H. Hamann[1], Gavin Shaddick[2], Kimme Hyrich[3], Amelia Green[4], Neil McHugh[4], John D. Pauling[4,5] on behalf of the BSRBR-RA Contributors Group

[1]Musculoskeletal Research Unit, Southmead Hospital, University of Bristol, Bristol, UK
[2]Mathematical Sciences, University of Exeter, Exeter, UK
[3]Centre for MSK Research, University of Manchester, Manchester, UK
[4] Department of Pharmacy and Pharmacology, University of Bath, Bath, UK
[5]Rheumatology, Royal National Hospital for Rheumatic Diseases, Bath, UK

Corresponding Author:

Dr Philip Hamann BMBS, BMedSci, MRCP, PhD
NIHR Clinical Lecturer in Rheumatology
Musculoskeletal Research Unit
Learning and Research Building
Southmead Hospital
University of Bristol
Bristol
BS10 5NB

Email: Philip.hamann@bristol.ac.uk

Keywords:

1. Rheumatoid arthritis
2. DAS28
3. CRP
4. ESR
5. Disease activity scores
6. BSRBR
7. Biologics
8. Gender
9. Age
10. BMI

Abstract:

Objectives: To evaluate determinants of discordance between DAS28-ESR and DAS28-CRP and resulting impact on disease activity stratification in rheumatoid arthritis (RA)

Methods: Paired DAS28-ESR and DAS28-CRP readings (n=31,074) were obtained from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA). Factors influencing discordance between DAS28-ESR and DAS28-CRP were evaluated alongside the resulting effect on disease activity stratification. The impact of gender adjustment to the DAS28-CRP was evaluated.

Results: DAS28-CRP scores were ~0.3 lower than DAS28-ESR overall, with greatest differences for women (-0.35) and patients over 50 years old (-0.34). Mean male DAS28-CRP scores were 0.15 less than corresponding DAS28-ESR scores. Discordance between DAS28-ESR and DAS28-CRP significantly impacted disease activity stratification at low disease activity (LDA) and remission thresholds (32.0% and 66.6% concordance respectively). Adjusting DAS28-CRP scores by gender significantly ($p < 0.001$) improved agreement with the DAS28-ESR.

Conclusion: Discordance between DAS28-ESR and DAS28-CRP is greatest for women and patients over 50 years of age, and influences disease activity stratification. The proposed gender adjusted DAS28-CRP improves inter-score agreement with DAS28-ESR, supporting more reliable disease activity stratification in treat-to-target approaches for RA.

Abstract Word Count: 181

Key Messages:

- This study shows that on average, DAS28-ESR generates scores 0.3 greater than the DAS28-CRP.
- The difference between the DAS28-CRP and DAS28-ESR is greater for women and patients over 50.
- Adjusting the DAS28-CRP according to gender significantly reduces inter-score differences with the DAS28-ESR.

Introduction:

Disease activity in rheumatoid arthritis (RA) is commonly measured using the 28-joint count disease activity score (DAS28), a composite index incorporating a tender joint count, swollen joint count, patient global assessment and markers of inflammatory response. The original DAS28 was developed and validated using the erythrocyte sedimentation rate (ESR) (1,2). Original development of the DAS28-CRP followed assessment of paired samples obtained from a relatively small cohort of 334 patients with subsequent wide adoption in clinical practice and trial settings (3). American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) do not differentiate between the two versions of the score when using disease activity thresholds. This results in the two versions of the score being used interchangeably in clinical practice (and observational studies which rely on data captured in clinical practice), with identical disease activity stratification thresholds adopted in assessment of disease activity, treatment response and treat-to-target approaches. Disparity in DAS28-CRP and DAS28-ESR values could also influence patient management where high-cost drug reimbursement is only permitted if specific disease activity thresholds are reached. In the UK access to biologics is dependent on patients having a DAS28 score of greater than 5.1 on two successive occasions at least one month apart (4). Therefore, discrepancies between scoring methods may delay the availability of biologic DMARDs to patients. Many studies have highlighted consistently lower DAS28-CRP compared to DAS28-ESR scores, at both lower levels of disease activity that form the focus of treat-to-target management (5-9) and high disease activity (10). It is acknowledged that ESR values are generally higher in females and increases with age (11), whilst the CRP is not affected by these factors. ESR and CRP levels may also be differentially affected by body mass index (BMI). Understanding the relative impact of gender, age and BMI on inter-score differences may help improve agreement between the DAS28-CRP and DAS28-ESR such that both instruments could be used interchangeably.

We report an analysis from the British Society of Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA) using real-world data, exploring discordance between the DAS28-CRP and DAS28-ESR, and resulting impact on disease activity stratification in RA. We propose that the DAS28-CRP should be adjusted depending on gender.

Methods:

Study population

The BSRBR-RA is a national, prospective, longitudinal, observational study examining long-term safety of biologic agents in patients with RA in the UK. Ethical approval was obtained from the Multicentre Research Ethics Committee for the North-West of England. All patients enrolled provided written informed consent.

Subject selection and data collection

The methods of the BSRBR-RA have been described previously (12). Patients treated with biologic therapy with concurrent measures of ESR and CRP were identified from the BSRBR-RA, enabling paired calculation of DAS28-ESR and DAS28-CRP using existing formulae (13). Data obtained at baseline and following treatment with biologic agents, was used in the initial cohort analysis. Data from patients taking tocilizumab were excluded due to specific effects of IL-6 on serum CRP levels (14).

Statistical analysis

The impact of age, baseline body mass index (BMI) and gender on concordance between DAS28-ESR and DAS28-CRP was assessed by dichotomising the group for age (≥or< 50yrs), gender, and stratifying BMI according to World Health Organization thresholds (15). A random effects model was used to allow for the possibility that ESR and CRP were not measured from the same blood sample. Age at enrollment to the BSRBR-RA was used where it was not possible to calculate the age at time when the DAS28 score was measured.

Agreement between the scores was compared using Bland-Altman statistics. Descriptive analysis was applied to compare disease stratification within accepted DAS28 disease activity thresholds. The cohort was subsequently subdivided according to gender. DAS28-CRP scores were differentially adjusted according to the inter-score differences identified in the initial analysis, and subsequent inter-score differences were compared. Kappa values and root mean squared error (RMSE) calculated the agreement and mean error of DAS28-CRP and subsequent adjusted DAS28-CRP scores (16). The differences in mean errors between the DAS28-ESR and DAS28-CRP or adjusted DAS28-CRP were compared using the Wilcoxon signed rank test.

Results:

Subject characteristics

Paired ESR and CRP values were available for 8,509 subjects, with 31,074 paired assessments (Table 1). The majority of subjects were female (76%), with mean age of 57.3 years (SD 12.2) and a mean baseline disease duration of 12.7 years (SD 9.6).

Discordance between DAS28-ESR and DAS28-CRP

The DAS28-CRP was on average 0.3 points lower than the corresponding DAS28-ESR for the whole cohort. When stratifying by age and gender, differences between the two scores were more pronounced for women and patients aged over 50 (0.35 points for both). The mean DAS28-CRP score in males was only 0.15 points less than the corresponding DAS28-ESR score. Mean inter-score differences did not alter when categorised by baseline BMI (~~Table 1~~Table 2).

Impact of disparity between DAS28-ESR and CRP on disease activity stratification

Disparity between the DAS28-ESR and DAS28-CRP had a significant impact on disease stratification, particularly within the low disease activity (LDA) category where the two scores only agreed in 32.0% of cases (~~Table 2~~Table 3). The DAS28-ESR classified fewer patients in remission compared with the DAS28-CRP, and more in high disease activity (Supplementary ~~Table 1~~Table 2).

Adjusting DAS28-CRP according to gender

Subdividing the cohort by gender and adjusting DAS28-CRP scores by +0.35 for females and +0.15 for men significantly reduced inter-score differences overall ($p < 0.001$ for females and males), and for age and BMI strata (~~Table 1~~Table 2). Inter-score disease activity classification improved for remission, low and moderate disease activities, with only a very minor reduction in agreement at high disease activity (3.9% and 0.7% for females and males respectively; ~~Table 2~~Table 3). RMSE reduced from 0.62 to 0.51 DAS28 points for females and 0.58 to 0.56 for men and kappa was increased for females (from 0.61 to 0.69) and males (from 0.66 to 0.69) when baseline DAS28-CRP scores were adjusted according to gender.

Discussion:

This study agrees with existing evidence suggesting DAS28-ESR and DAS28-CRP should not be viewed as interchangeable outcome measures, highlighting the limitations of doing so, with important consequences for

clinical and research practice (5-10). We have proposed a novel and practical method for improving agreement between the two indices that could be applied in future observational studies and clinical practice where both methods have been applied at different time-points.

Initial development of the DAS28-CRP by Fransen *et al.*, which included data from 334 patients, used linear regression and high Pearson correlation coefficient to suggest equivalence with the DAS28-ESR. However, at that time, agreement analysis was not undertaken (3). Subsequent analyses by Wells *et al.* (17) demonstrated the DAS28-CRP to be a valid outcome measure, although inter-score discrepancies were identified. Consequently, whilst correlation between the scores was high, equivalence and interchangeability was not demonstrated. Disparity between DAS28-ESR and DAS28-CRP has led some to propose applying lower disease activity thresholds for the DAS28-CRP (6,7,10). However, this approach does not take into account the differential impact of age and gender between the two DAS28 scores. Furthermore, changing disease activity thresholds of the DAS28-CRP, would necessitate updating all guidance where reference is made only to the 'DAS28' without specification as to the version used.

We have demonstrated that variation in equivalence between the two scores is most pronounced for older patients and women (demographics representing the majority of the RA population) and at lower disease activity levels (the target for most treatment strategies). This discordance precludes easy comparison of outcomes of studies that have adopted different versions of the DAS28. The impact of BMI was lower than anticipated and correction for BMI to improve agreement between the two scores is not necessary. It is possible that other factors (including comorbidities) may affect the relationship between ESR and CRP measurements. However, limiting the additional data required to improve inter-score agreement means these findings can be translated to use in clinical and research settings.

We propose that adjusting DAS28-CRP scores by +0.35 points for females and +0.15 points for males would significantly improve inter-score agreement, and allow existing disease activity thresholds to be used without modification. This adjustment takes into account observed biological differences in ESR levels between females and males and is straightforward and practical.

Improvement in agreement of disease activity stratification at lower disease activity thresholds is achieved at the expense of a minor reduction in agreement at HDA; the effect of which would be to encourage more active

treatment for patients with higher disease activity, in line with current treatment paradigms. Adjustment of the DAS28-CRP based on age was considered, however the time-varying nature of age makes this a less practical adjustment to the score.

A potential limitation is that we used a single cohort for our study. However, patients included in the BSRBR-RA are enrolled from across the UK, representing a broad population and spectrum of RA management. The cohort is mainly of Caucasian ethnicity, which may influence ESR and CRP relationships differently compared with other ethnicities.(8,9) The main cohort included patients on biological agents recruited to a registry which may introduce selection bias, although it is unlikely this would impact on ESR/CRP comparisons. It is possible unknown confounders may influence whether an individual has both an ESR and CRP test undertaken rather than only one. There were some missing data, although there were no significant demographic differences between missing and complete groups (Supplementary ~~Table 2~~Table 3).

Our findings suggest the DAS28-ESR and DAS28-CRP should not be used interchangeably when stratifying disease activity. Gender influences inter-score agreement, and adjustment of the DAS28-CRP according to gender significantly improves inter-score reliability.

Acknowledgments

The authors acknowledge the enthusiastic collaboration of all consultant rheumatologists and their specialist nurses in the UK in providing the data (visit www.bsrbr.org for a full list of contributors). The authors would like to gratefully acknowledge the support of the National Institute for Health Research, through the Comprehensive Local Research Networks at participating centres. In addition, the authors acknowledge support from the BSR Executive, the members of the BSRBR Registers Committee and the BSRBR Project Team in London for their active role in enabling the register to undertake its tasks. The authors also acknowledge the seminal role of the BSR Clinical Affairs Committee for establishing national biological guidelines and recommendations for such a register. Finally, the authors would like to acknowledge the Arthritis Research UK Centre for Epidemiology who provided the infrastructure support for the study.

This work was conducted on behalf of BSR and Dr Hamann would like to thank BSR for its help and support.

Conflict of interest statement

Professor Hyrich has received honoraria of less than $10,000 from Pfizer and Abbvie in the past two years.

Dr Hamann has received honoraria of less than $10,000 from Decision Resources Group Ltd and provided consultancy for ~~Propagator~~ Living With Ltd. software company over the past year for development of a health-related mobile phone application.

None of the other authors have any conflicts of interest to declare.

Funding

This work was supported by the British Society for Rheumatology (BSR). The BSR commissioned the BSR Biologics Register in rheumatoid arthritis (BSRBR-RA) as a UK wide national project to investigate the safety of biologic agents in routine medical practice. KH is the principal investigator. BSR receives restricted income from UK pharmaceutical companies, including Abbvie, Celltrion, Hospira, MSD, Pfizer, SOBI, Samsung, UCB and Roche. This income finances a wholly separate contract between the BSR and the University of Manchester. The principal investigator and the BSRBR-RA team at the University of Manchester have full academic freedom and are able to work independently of pharmaceutical industry influence. All decisions concerning analyses, interpretation and publication are made autonomously of any industrial contribution. Members of the BSRBR-RA University of Manchester team, BSR trustees, committee members and staff complete an annual declaration in relation to conflicts of interest. All relevant information regarding serious adverse events outlined in the manuscript have been reported to the appropriate pharmaceutical company as per the contractual agreements/ standard operating procedures.

Dr Hamann's research was funded by the BSR through the Clinical Research Fellowship in Musculoskeletal Epidemiology.

References

1. Prevoo ML, van 't Hof MA, Kuper HH, Van Leeuwen MA, Van de Putte LB, Van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995 Jan;38(1):44–8.

2. van Gestel AM, Haagsma CJ, Van Riel PL. Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. Arthritis Rheum. 1998 Oct;41(10):1845–50.

3. Fransen J, Welsing P, De Keijzer R, Van Riel PCLM. Disease activity scores using C-reactive protein: CRP may replace ESR in the assessment of RA disease activity. Ann Rheum Dis. 2003. Available from: http://www.abstracts2view.com/eular/view.php?nu=EULAR03L1_2003THU0138

4. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed. NICE; 2013 Aug 28; 1–736.

5. Siemons L, Vonkeman HE, Klooster ten PM, van Riel PLCM, van de Laar MAFJ. Interchangeability of 28-joint disease activity scores using the erythrocyte sedimentation rate or the C-reactive protein as inflammatory marker. Clin Rheumatol. 2014 Jun;33(6):783–9.

6. Fleischmann R, van der Heijde D, Koenig AS, Pedersen R, Szumski A, Marshall L, et al. How much does Disease Activity Score in 28 joints ESR and CRP calculations underestimate disease activity compared with the Simplified Disease Activity Index? Ann Rheum Dis. 2014 Aug 20;annrheumdis–2013–204920.

7. Inoue E, Yamanaka H, Hara M, Tomatsu T, Kamatani N. Comparison of Disease Activity Score (DAS)28-erythrocyte sedimentation rate and DAS28- C-reactive protein threshold values. Ann Rheum Dis. 2007 Mar;66(3):407–9.

8. Matsui T, Kuga Y, Kaneko A, Nishino J, Eto Y, Chiba N, et al. Disease Activity Score 28 (DAS28) using C-reactive protein underestimates disease activity and overestimates EULAR response criteria compared with DAS28 using erythrocyte sedimentation rate in a large observational cohort of rheumatoid arthritis patients in Japan. Ann Rheum Dis. 2007 Sep;66(9):1221–6.

9. Tamhane A, Redden DT, McGwin G, Brown EE, Westfall AO, Reynolds RJ, et al. Comparison of the disease activity score using erythrocyte sedimentation rate and C-reactive protein in African Americans with rheumatoid arthritis. J Rheumatol. 2013 Nov;40(11):1812–22.

10. Fleischmann RM, van der Heijde D, Gardiner PV, Szumski A, Marshall L, Bananis E. DAS28-CRP and DAS28-ESR cut-offs for high disease activity in rheumatoid arthritis are not interchangeable. RMD Open. 2017;3(1):e000382.

11. Wetteland P, Røger M, Solberg HE, Iversen OH. Population-based erythrocyte sedimentation rates in 3910 subjectively healthy Norwegian adults. A statistical study based on men and women from the Oslo area. J Intern Med. 1996 Sep;240(3):125–31.

12. Watson K, Symmons D, Griffiths I, Silman A. The British Society for Rheumatology biologics register. Ann Rheum Dis. 2005 Nov;64 Suppl 4:iv42–3.

13. DAS28 - How to calculate the DAS28 [Internet]. das-score.nl. [cited 2016 Sep 20]. Available from: http://www.das-score.nl/das28/en/difference-between-the-das-and-das28/how-to-measure-the-das28/how-to-calculate-the-das28.html

14. Eklund CM. Chapter 5 - Proinflammatory Cytokines in CRP Baseline Regulation. 1st ed. Vol. 48, Adv Clin Chem. 2009. 26 p.

15. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. Vol. 894, World Health Organization technical report series. 2000 pp. i–xii–1–253.

16. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977.

17. Wells G, Becker J-C, Teng J, Dougados M, Schiff M, Smolen J, et al. Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. Ann Rheum Dis. 2009 Jun;68(6):954–60.