Thresholds for the 28-joint disease activity score (DAS28) using C-reactive protein are lower compared to DAS28 using erythrocyte sedimentation rate in early rheumatoid arthritis

B. Kuriya[1], O. Schieir[2], D. Lin[1], J. Xiong[1], J. Pope[3], G. Boire[4], B. Haraoui[5], J.C. Thorne[6], D. Tin[6], C. Hitchon[7], S. Jamal[8], E. Keystone[1], V. Bykerk[1,9], for the CATCH Investigators

[1]Sinai Health System, University of Toronto, Canada; [2]Division of Epidemiology, University of Toronto, Dalla Lana School of Public Health, Toronto, Canada; [3]St. Josephs Health Care, University of Western Ontario, London, Canada; [4]Universite de Sherbrooke, Sherbrooke, Canada; [5]Institut de Rhumatologie, Montreal, Canada; [6]Southlake Regional Health Centre, Newmarket, Canada; [7]University of Manitoba, Winnipeg, Canada; [8] Vancouver General Hospital, University of British Columbia, Canada; [9]Hospital for Special Surgery, New York, USA.

Abstract

Objective

The 28-Joint Disease Activity Score (DAS28) using C-reactive protein (CRP) and DAS28 using erythrocyte sedimentation rate (DAS28-ESR) may not be interchangeable. We sought to compare and estimate optimal thresholds for the DA28-CRP for use in early rheumatoid arthritis (ERA).

Methods

Patients from the Canadian Early Arthritis Cohort with baseline and 12 months' data for both DAS28-ESR and DAS28-CRP were examined for correlations and differences between DAS28-CRP and DAS28-ESR across their range of values. Receiver operating characteristic analysis identified thresholds for DAS28-CRP that best corresponded to established thresholds for the DAS28-ESR using the total sample, then stratified by age and sex. Agreement between DAS28-CRP and DAS28-ESR thresholds was assessed with the kappa statistic.

Results

The sample included 995 patients with mean (SD) age of 53.7 (14.5) years, 5.8 (2.9) months of symptom duration and 74% were female. DAS28-CRP and DAS28-ESR scores were highly correlated (r= 0.92, p<0.0001), however DAS28-CRP values were consistently lower than DAS28-ESR values. Calculated thresholds for DAS28-CRP were lower with 2.5 for remission, 2.9 for low disease activity, and 4.6 for high disease activity but showed moderate agreement with the DAS28-ESR thresholds (kappa=0.70).

Conclusion

In this large sample of ERA patients, newly estimated thresholds for DAS28-CRP were consistently lower than DAS28-ESR thresholds across the spectrum of disease activity. This may have important clinical implications if inflammatory markers are used interchangeably. Additional external validation of our findings is needed.

Key words

rheumatoid arthritis, disease activity, remission

Bindee Kuriya, MD, MS, FRCP(C)
Orit Schieir, PhD
Daming Lin, PhD
Juan Xiong, MSc
Janet Pope, MD, MPH, FRCPC
Gilles Boire, MD, MS, FRCPC
Boulos Haraoui, MD, FRCPC
John Carter Thorne, MD, FRCPC
Diane Tin, BSc. Phm
Carol Hitchon, MD, MSc, FRCPC
Shahin Jamal, MD, MSc, FRCPC
Edward Keystone, MD, FRCPC
Vivian Bykerk, MD, FRCPC

Please address correspondence and reprint requests to:
Dr Bindee Kuriya,
Sinai Health System,
The Joseph and Wolf Lebovic Building,
60 Murray Street, Room 2-008,
Toronto, M5T 3L9 Ontario, Canada.
E-mail: bindee.kuriya@sinaihealthsystem.ca

Received on October 24, 2016; accepted in revised form on January 30, 2017.

Competing interests: none declared.

Introduction

Rheumatoid arthritis (RA) is a complex inflammatory disease requiring multiple parameters to assess disease activity and monitor therapeutic response.

The Disease Activity Score 28 joints (DAS28) is a widely used and validated outcome for measuring RA disease activity (1). It is a composite index that incorporates the erythrocyte sedimentation rate (ESR), which is a parameter of chronic inflammation.

C-reactive protein (CRP) is a more acute indicator of inflammation and less affected by patient-specific variables than ESR (2). Thus, CRP may be a preferred marker for clinical use, and is often used to generate a DAS28 score using the same cut-offs established for the DAS28-ESR (2, 3).

Studies have reported that DAS28-CRP yields lower scores than DAS28-ESR and have cautioned that established disease state thresholds may not be interchangeable with DAS28-CRP (4-8). Results from these studies were predominantly based on select geographic samples with established RA, which may not be representative of other clinical settings (9-11). A recent analysis also suggested that DAS28-ESR cut-off values should not be applied to DAS28-CRP (12). However, this study was based on pooled data from clinical trials with patient characteristics not generalisable to routine clinical practice. In an era where treat-to-target approaches and access to biologics are frequently contingent on DAS28 categories of disease activity, even small discrepancies in measurement can have important clinical implications.

The objective of this study was to estimate and validate previously proposed new thresholds for DAS28-CRP remission, low, moderate and high disease activity states in an early rheumatoid arthritis (ERA) cohort.

Materials and methods

Participants

Study participants were enrolled in the Canadian early ArThritis CoHort (CATCH), a large multicenter cohort study of patients with early inflammatory arthritis. CATCH participants undergo standardised clinical and laboratory assessments and treatment with disease modifying anti-rheumatic drugs is provided at the discretion of the rheumatologist, generally following a treat-to-target approach. The present study included ERA patients enrolled in CATCH since inception (2007) through October 2014, and data to calculate both DAS28-ESR and DAS28-CRP scores at baseline and 12 month follow up. ESR levels were determined by the Westergren method (mm/hour) and serum CRP levels were obtained (mg/L). Patients were classified into disease activity states according to established thresholds for REM (DAS28-ESR <2.6), LDA (DAS28-ESR ≤3.2), MDA (3.2< DAS28-ESR ≤5.1) and HDA (DAS28-ESR >5.1).

Statistical analyses

The relationship between composite DAS28-ESR and DAS28-CRP measures was estimated with Pearson's correlation (r) coefficient.

Thresholds for the DAS28-CRP that best corresponded to established DAS28-ESR thresholds were identified by combining results from multiple methods. We created receiver operator characteristic (ROC) curves by plotting the sensitivity and specificity of the DAS28-CRP at every possible cut-off point, and maximised the best trade-off between sensitivity and specificity (13). Although sensitivity and specificity are important measures of diagnostic accuracy, they cannot help estimate the probability of disease state in individual patients. Therefore, we calculated positive predictive values (PPV), negative predictive values (NPV) and likelihood ratios (14, 15). Ultimately, the optimal DAS28-CRP cut offs were determined based on the ROC analyses (maximising area under the curve) and highest positive predictive values.

The kappa statistic was used to assess classification agreement overall between DAS28-ESR and DAS28-CRP values at baseline and month 12 using a weighted kappa coefficient (16). Kappa statistics were also used to compare agreement between newly calculated thresholds for the DAS28-CRP and established thresholds for the DAS28-ESR (17). Statistical significance was

defined as $p<0.05$. All analyses were performed using SAS® (v. 9.3).

Results

The sample included 995 CATCH participants with ERA. A detailed participant flow diagram is presented as Figure 1. Patients who were excluded due to missing data were not significantly different.

Sample characteristics at baseline are presented in Table I. Participants were predominantly Caucasian (83%), female (74%), with mean (SD) age of 54 (15) years and symptom duration 5.8 (2.9) months. The majority of patients were in MDA or HDA and mean (SD) DAS28-ESR of 5.1 (1.4) was higher than mean DAS28-CRP 4.7 (1.3).

Composite DAS28-ESR and DAS28-CRP measures were strongly correlated (baseline Pearson's r of 0.92, $p<0.001$)

Table II displays the optimal cut-off values for DAS28-CRP and their associated diagnostic measures of accuracy. The derived DAS28-CRP REM value was ≤2.5, DAS28-CRP LDA was ≤2.9, DAS28-CRP MDA was ≤4.6 and DAS28-CRP HDA was >4.6. DAS28-CRP remission and LDA thresholds were lower than DAS28-ESR category thresholds, most notably for women and those greater than 60 years of age (data not shown). PPV was lowest for the remission threshold (range 74% to 95%) but PPV remained high for LDA and HDA, even when stratified by age and sex.

Overall, there was moderate agreement between established DAS28-ESR and proposed DAS28-CRP thresholds using month 12 data (κ=0.70). Total agreement was substantial for patients over the age of 60 (κ= 0.71) for patients less than 60 years of age (= 0.73), for men (κ= 0.70) and for women (κ= 0.73).

Discussion

In this inception ERA cohort, we found that disease activity based on DAS28-CRP yielded lower thresholds compared to DAS28-ESR scores. Using the DAS28-ESR as the gold standard, we estimated DAS28-CRP thresholds of 2.5, 2.9 and 4.6 for remission, low and high disease activity states, respectively.

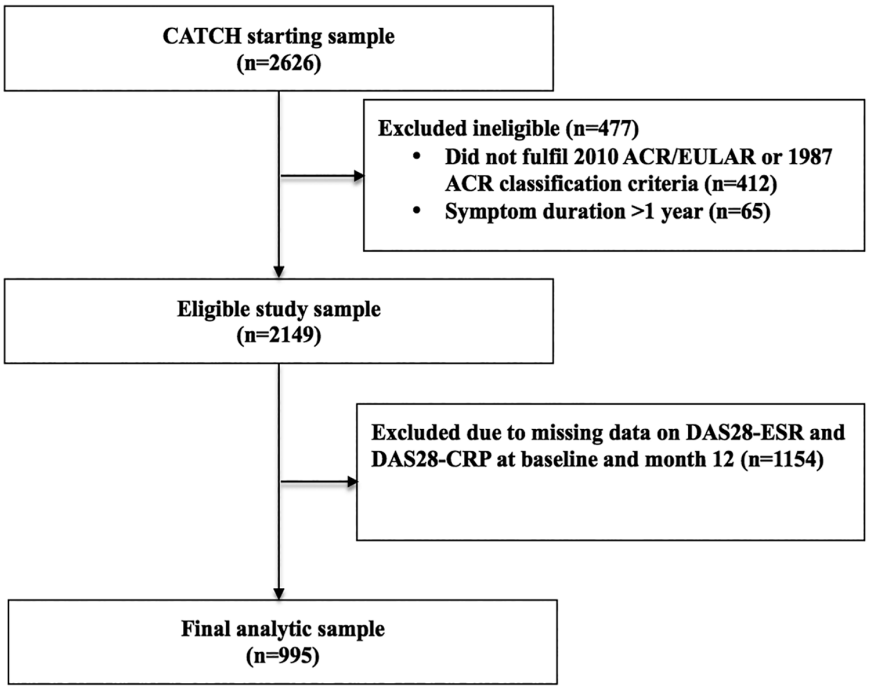

Fig. 1. CATCH participant flow diagram.
CATCH: Canadian early rheumatoid ArThritis CoHort; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; DAS28, Disease Activity Score 28 joints; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Table I. Baseline characteristics of CATCH participants (n=995)

Demographic characteristics	Mean (SD) or frequency (%)
Age (years)	53.7 (14.5)
Female	738 (74%)
Caucasian	822 (83%)
Current smoker	163 (16%)
Ex-smoker	397 (40%)
ever smoker	435 (44%)
High school education	447 (45%)
Income ≤ $50,000 (n=653)	373 (57%)
Symptom duration (months)	5.8 (2.9)
Disease activity measures	
TJC-28	9 (7)
SJC-28	8 (6.0)
PTGA (0-10 cm scale)	5.7 (2.9)
MDGA (0-10 cm scale)	4.9 (2.5)
ESR (mm/hr)	27.1 (21.6)
CRP (mg/L)	14.3 (17.9)
DAS28-ESR	5.1 (1.4)
DAS28-CRP	4.7 (1.3)
Initial treatment	
Conventional synthetic DMARD monotherapy	437 (44%)
Conventional synthetic DMARD combination therapy	449 (45%)
Biologic DMARD	31 (3%)
Corticosteroids	
Oral (po)	293 (29%)
Parenteral (IA/IM)	301 (30%)

DAS28: Disease Activity Score 28 joints; DMARD: disease-modifying anti-rheumatic drug; ESR: erythrocyte sedimentation rate; MDGA: physician global assessment of disease; PTGA: patient global assessment of disease; SJC-28: swollen joint count out of 28 joints; TJC-28: tender joint count out of 28 joints. *Initial treatment reflects therapy started only after cohort entry (within first 3 months).

Table II. Diagnostic measures for newly calculated thresholds for DAS28-C-reactive protein disease states using Disease Activity Score 28 (DAS28)-erythrocyte sedimentation rate as the standard among the whole group, and stratified by age and sex.

Disease activity states	DAS28-ESR	DAS28-CRP	Sensitivity (%)	Specificity (%)	AUC	PPV (%)	NPV (%)	Positive LR	Negative LR
Total sample									
Remission	2.6	2.5	87	84	0.71	82	88	5.4	0.15
Low disease activity	3.2	2.9	90	84	0.75	85	90	5.6	0.11
High disease activity	5.1	4.6	86	93	0.78	92	87	11.6	0.16
Women									
Remission	2.6	2.5	88	83	0.72	80	91	5.5	0.13
Low disease activity	3.2	2.9	91	82	0.74	88	88	5.2	0.11
High disease activity	5.1	4.6	87	92	0.79	91	88	10.5	0.14
Men									
Remission	2.6	2.5	84	85	0.68	88	80	5.5	0.19
Low disease activity	3.2	2.9	88	90	0.75	95	77	8.8	0.13
High disease activity	5.1	4.6	81	95	0.77	95	83	16.9	0.20
Age > 60 years									
Remission	2.6	2.5	89	80	0.67	74	92	4.5	0.14
Low disease activity	3.2	2.9	94	84	0.89	92	90	6.09	0.16
High disease activity	5.1	4.6	85	92	0.77	88	88	9.9	0.07
Age ≤ 60 years									
Remission	2.6	2.5	86	86	0.73	87	86	6.4	0.16
Low disease activity	3.2	2.9	88	84	0.72	90	81	5.4	0.14
High disease activity	5.1	4.6	86	93	0.79	94	85	12.9	0.15

DAS28: Disease Activity Score 28 joints; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; AUC: area under the curve; PPV: positive predictive value; NPV: negative predictive value; LR; likelihood ratio.

The results from the present study are consistent with others showing that CRP-based DAS28 disease activity thresholds are lower than ESR-based DAS28 scores (5, 6, 9, 11, 18, and 19). We independently arrived at a similar DAS28-CRP cut-off of 2.4 for REM and the same value of 2.9 for LDA that Fleischmann *et al*. proposed (12). However, our analysis was unique by using two time points- baseline and month 12- and we were able to demonstrate how test characteristics and resultant cut-off points varied over time with attainment of different disease states. Our HDA cut-off of 4.9 was identical to Castrejón *et al*. but our results differed with regards to lower sensitivity for CRP-based definitions of REM, especially when using baseline values for calculation, where prevalence of REM was lowest. Translated for use in real-world settings, lower sensitivity equates to the risk that some patients in REM may be missed, but the high PPV ensures that the percentage of patients identified as being in REM by the DAS28-CRP are actually in REM according to the gold standard DAS28-ESR definition. Sensitivity and PPV for DAS28-CRP values increased for MDA and HDA, suggesting it may be interchanged with the DAS28-ESR more reliably in these states. However, it should be cautioned that the lower threshold of 4.6 for HDA could have important treatment implications, especially in settings where access to biologics is contingent on documented DAS28 >5.1.

While absolute differences between established ESR disease activity thresholds and DAS28-CRP thresholds proposed by the present study may appear small, it is important to consider that the DAS28 is a continuous composite measure, and that if DAS28-ESR thresholds were applied to the measure calculated with CRP, then a significant proportion of patients could potentially be misclassified. These findings raise the question about the interchangeability of these indices, where decisions about maintaining or escalating treatment are formulated in a treat-to-target approach aiming for remission or low disease state based on ESR thresholds. In many current day clinical trials, strategies testing withdrawal of therapy based on achievement of one of these states would also be affected depending on the measure used.

The question remains whether DAS28-CRP truly underestimates disease activity or whether the ESR-based calculation overestimates activity because of biological mechanisms (*e.g*. age, gender, chronicity of inflammation, red blood cell size etc.) known to preferentially affect ESR but not CRP values (2). In fact, we found that differences in mean values between DAS28-ESR and DA28-CRP were greater for females and older patients which are consistent with other reports (5, 9, and 10).

General agreement between DAS28-ESR and DAS28-CRP has been described by others, but our study was strengthened by the addition of ROC curves to estimate optimal cut-off values for the CRP method and calculation of the clinically relevant PPV, NPV values and likelihood ratios. We attempted to study the influence of age and sex on DAS28, which has been evaluated in established RA but not strictly in an early rheumatoid arthritis population, to our knowledge (20). Unlike other studies, we took the additional step of comparing findings at two time points and demonstrated how it may be misleading to apply remission thresholds before patients have had optimal duration of treatment. As suggested by Fleis-

chmann *et al*., we took care to select baseline rather follow-up data where a greater proportion of patients were available for analysis to allow a correct determination of DAS28-CRP cut-offs for MDA and HDA (12). A further strength was our large sample of participants that is representative of usual care across Canada. Our main limitation was the proportion of missing data for the sample that met study eligibility criteria but we did demonstrate these patients were comparable to those who were included in the analysis.

In conclusion, DAS28-CRP and DAS28-ESR were strongly correlated, but threshold values for DAS28-CRP were consistently lower than DAS28-ESR thresholds across the spectrum of disease activity and should not be interchangeable. Additional external validation of our findings in other ERA cohorts is needed.

Acknowledgements

We would like to acknowledge the following individuals: Ms Franci Sniderman (study manager), Dawn Richards (patient representative) and all of the CATCH investigators and participants.

The CATCH Investigators

Vivian Bykerk, Boulos Haraoui, Janet Pope, Gilles Boire, Murray Baron, Susan Bartlett, John Carter Thorne, Carol Hitchon, Edward C. Keystone, William Bensen, Lawrence Rubin, Louis Bessette,Bindee Kuriya, Pooneh Akhavan, Maggie Larche, Ines Colmegna, Vandana Ahluwahlia, Christopher Penney, Christopher Lyddell, Alice Klinkhoff, Shahin Jamal, Michel Zummer.

References

1. ALETAHA D, WARD MM, MACHOLD KP, NELL VPK, STAMM T, SMOLEN JS: Remission and active disease in rheumatoid arthritis: defining criteria for disease activity states. *Arthritis Rheum* 2005; 52: 2625-36.
2. CROWSON CS, RAHMAN MU, MATTESON EL: Which measure of inflammation to use? A comparison of erythrocyte sedimentation rate and C-reactive protein measurements from randomized clinical trials of tocilizumab in rheumatoid arthritis. *J Rheumatol* 2009; 36: 1606-10.
3. FRANSEN J, WELSING PMJ, DE KEIJZER RMH, VAN RIEL PLCM: Disease activity scores using C-reactive protein: CRP may replace ESR in the assessment of RA disease activity. *Ann Rheum Dis* 2003; 62 (Suppl. 1): 151-8.
4. INOUE E, YAMANAKA H, HARA M, TOMATSU T AND KAMATANI N: Comparison of Disease Activity Score (DAS) 28-erythrocyte sedimentation rate and DAS28- C-reactive protein threshold values. *Ann Rheum Dis* 2007; 66: 407-9.
5. SIEMONS L, VONKEMAN HE, TEN KLOOSTER PM, VAN RIEL PL, VAN DE LAAR MA: Interchangeability of 28-joint disease activity scores using the erythrocyte sedimentation rate or the C-reactive protein as inflammatory marker. *Clin Rheumatol* 2014; 33: 783-9.
6. CASTREJÓN I, ORTIZ AM, GARCÍA-VICUÑA R *et al*.: Are the C-reactive protein values and erythrocyte sedimentation rate equivalent when estimating the 28-joint disease activity score in rheumatoid arthritis? *Clin Exp Rheumato*l 2008; 26: 769-75.
7. WELLS G, BECKER JC, TENG 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* 2008; 68: 954-60.
8. HENSOR EM, EMERY P, BINGHAM SJ, CONAGHAN PG, YEAR CONSORTIUM: Discrepancies in categorizing rheumatoid arthritis patients by DAS-28(ESR) and DAS-28(CRP): can they be reduced? *Rheumatology* (Oxford) 2010; 49: 1521-29.
9. MATSUI T, KUGA Y, KANEKO A *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; 66: 1221-26.
10. TAMHANE A, REDDEN DT, MCGWIN JR *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; 40: 1812-22.
11. CASTREJÓN I, ORTIZ AM, TOLEDANO E *et al*.: Estimated cutoff points for the 28-joint disease activity score based on C-reactive protein in a longitudinal register of early arthritis. *J Rheumatol* 2010; 37: 1439-43.
12. FLEISCHMANN R, VAN DER HEIJDE D, KOENIG AS *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* 2015; 74: 1132-7.
13. AKOBENG AK: Understanding diagnostic tests 3: Receiver operating characteristic curves. *Acta Paediatr* 2007; 96: 644-7.
14. AKOBENG AK: Understanding diagnostic tests 1: sensitivity, specificity and predictive values. *Acta Paediatr* 2007; 96: 338-41.
15. AKOBENG AK: Understanding diagnostic tests 2: likelihood ratios, pre- and post-test probabilities and their use in clinical practice. *Acta Paediatr* 2007; 96: 487-91.
16. JAKOBSSON U, WESTERGREN A: Statistical methods for assessing agreement for ordinal data. *Scand J Caring Sci* 2005; 19: 427-31.
17. LANDIS JR, KOCH GG: The measurement of observer agreement for categorical data. *Biometrics* 1977; 33: 159-74.
18. SON KM, KIM SY, LEE SH, YANG CM, SEO YI, KIM HA: Comparison of the disease activity score using the erythrocyte sedimentation rate and C-reactive protein levels in Koreans with rheumatoid arthritis. *Int J Rheum Dis* 2015 Jul 22 [Epub ahead of print]
19. SENGUL I, AKCAY-YALBUZDAG S, INCE B, GOKSEL-KARATEPE A, KAYA T: Comparison of the DAS28-CRP and DAS28-ESR in patients with rheumatoid arthritis. *Int J Rheum Dis* 2015; 18: 640-5.
20. RADOVITS BJ, FRANSEN J, VAN RIEL PL, LAAN RF: Influence of age and gender on the 28-joint Disease Activity Score (DAS28) in rheumatoid arthritis. *Ann Rheum Dis* 2008; 67: 1127-31.