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Concise report

DAS28, CDAI and SDAI cut-offs do not translate the same information: results from the Rheumatic Diseases Portuguese Register Reuma.pt

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Abstract

Objectives. The 28-joint DAS (DAS28), clinical disease activity index (CDAI) and simplified disease activity index (SDAI) are indices frequently used to assess disease activity in RA patients. Cut-off values were defined to classify the states of RA disease activity: remission, low, moderate and high. The aim of this work was to assess disease activity states classified by DAS28, CDAI and SDAI and to analyse their agreement in the Rheumatic Diseases Portuguese Register Reuma.pt.

Methods. A total of 2795 patients and 14 440 visits were selected from Reuma.pt for analysis. Pearson's correlation coefficients (PCCs) were calculated for the three indices. McNemar's chi-squared tests, PCCs and kappa statistics were performed to analyse and compare the distribution of visits among all disease activity states and indices.

Results. A strong correlation was found between the three indices throughout the 14 440 visits: $r = 0.874$ for DAS28/CDAI, $r = 0.877$ for DAS28/SDAI and $r = 0.984$ for CDAI/SDAI (all PCCs with $P < 0.0001$). However, when categorization in the different disease activity states was analysed, McNemar's chi-squared tests and PCCs revealed significant disagreement between the cut-offs of the three indices.

Conclusion. DAS28, CDAI and SDAI cut-offs do not translate into the same clinical information in Reuma.pt. Although this might be expected for the original DAS28 cut-offs, when compared with CDAI and SDAI significant disagreement was also found for the DAS28 modified cut-offs. For visits where patients are in CDAI or SDAI remission, we also find disagreement between these two indices, which may contradict previous conclusions that acute phase reactants add little to composite disease activity indices for RA.

Key words: rheumatoid arthritis, disease activity, outcome measures, disease activity score.

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CLINICAL SCIENCE

Introduction

Routine use of composite measures to assess RA disease activity has become standard practice in rheumatology [1]. The 28-joint DAS (DAS28) is the most widely used instrument in both clinical trials and daily practice [2]. This is a clinical index of RA disease activity that combines information on swelling and tenderness from 28 joints, ESR and an optional patient global assessment (PGA) of general health on a 0–100 mm visual analogue scale (VAS) [3]. This tool has been extensively validated for use in clinical trials in combination with the European League Against Rheumatism (EULAR) response criteria [4–8]. In 2003 an alternative formulation of the DAS28 based on CRP levels (DAS28-CRP) instead of ESR was developed [9]. However, the DAS28-CRP has not been formally validated and several studies concluded that the two indices are strongly, although not perfectly, correlated [10–12].

The simplified disease activity index (SDAI) [13] and the clinical disease activity index (CDAI) [14] were developed and validated more recently [15]. The SDAI is the numerical sum of five outcome parameters: tender and swollen joint counts (assessing 28 joints), CRP (in mg/dl) and PGA on a 0–10 cm VAS. This index has recently gained more relevance due to its inclusion in the ACR/EULAR remission criteria [16]. The CDAI includes the same components except CRP.

Most of the clinical implications of using these indices lie around the cut-offs established to classify the states of RA disease activity: remission, low, moderate and high. For each one of these states the DAS28, CDAI and SDAI cut-offs have been published [2, 15, 17, 18].

The main aim of this work was to assess the level of agreement of disease activity states classified by cut-offs with DAS28, CDAI and SDAI in clinical practice using Reuma.pt, the Rheumatic Diseases Portuguese Register.

Methods

Analyses were performed using Reuma.pt, from the Portuguese Society of Rheumatology. Reuma.pt was approved by the National Board for Personal Data Protection and local ethics committees. All included patients signed an informed consent form for registration and use of their anonymized data.

Patients and visits

All RA patients registered in Reuma.pt [19] fulfil the 1987 ACR criteria for the diagnosis of RA [20]. Our study focused on clinical visits registered up to September 2013. Registered visits having all parameters required to enable calculation of DAS28, CDAI and SDAI scores were included. These criteria were met by a total of 14 440 visits from 2795 patients. To assess internal consistency we also generated and analysed nine other subsets of data: a subset containing 2795 randomly selected visits (one visit per patient), another one containing the visits where the patient is exposed to biologic treatment, a third one containing the visits where the patient is not exposed to biologic treatment and, finally, six other subsets (one for each centre with at least 1000 visits) containing the visits of a single centre.

Statistical analysis

We started by calculating Pearson's correlation coefficients (PCCs) between all disease activity scores as continuous variables, for the whole dataset, without considering cut-offs. T

o assess the cut-off agreement we started by using the weighted quadratic kappa statistics with $\kappa = 4$. The equivalence of the cut-offs was further investigated by calculating the PCCs within each group of visits defined by the cut-offs of the two classifications systems included in each analysis. Finally, we dichotomized our multidimensional space containing four disease activity states in order to investigate agreement on 2×2 contingency tables. This dichotomization resulted in three different bi-dimensional statistical analyses: analysis of the visits where patients are in remission *vs* visits where patients are not in remission, analysis of the visits where patients are in remission or a low disease activity state *vs* moderate or high disease activity and analysis of the visits where patients are not in a high disease activity state *vs* high disease activity.

For each one of these 2×2 contingency tables, we used McNemar's chi-squared tests with continuity correction to test the significance of differences between the proportions of visits as classified by each of the compared indices. We then calculated kappa statistics ($\kappa = 2$) for each of the 2×2 contingency tables.

Results

Descriptive statistics

The eligibility criteria were met by a total of 14 440 visits from 2795 patients (82.83% women). The mean elapsed time between disease onset and the date of diagnosis was ~2.23 years (S.D. 4.44). A total of 1377 patients (49.27%) had never been exposed to biologic treatment and the remainder had at least one visit under this type of treatment. The mean elapsed time between the first and last selected visit was about 19.05 months (S.D. 25.12). Table 1 presents the demographic and clinical characteristics of the enrolled patients. The mean number of visits per patient was 5.17 (S.D. 5.88). A total of 3380 visits (23.41%) were from patients who were never exposed to biologic treatment, 354 visits (2.45%) preceded the start of biologic treatment, 3836 visits (26.57%) were within 2 years of starting biologic treatment and 6344 visits (43.93%) occurred $\geqslant$2 years after initiation of biologic treatment. Five hundred and twenty-six visits (3.64%) occurred after initiation of biologic treatment but patients were not exposed to biologic drugs at those visits, regardless of a posterior restart or not.

In September 2013 there were 30 580 visits from RA patients registered in Reuma.pt. For 21 471 visits (70.21%) we were able to calculate the DAS28, but for only 14 440 visits was it possible to calculate the three indices under comparison. In order to validate whether

Table 1 Patient characteristics

	At first visit			At last visit		
	n	Mean	S.D.	*n*	Mean	S.D.
Age, years	2795	57.2	13.6	2795	58,8	13,4
Disease duration, years	2430	11.7	9.7	2430	13,4	9,8
Patients with disease duration <24 months	252			129		
Patient global assessment (100 mm)	2795	44.2	26.5	2795	37,1	25,5
Physician global assessment (100 mm)	2795	32.1	24.3	2795	23,2	20,1
Tender joints (0–28)	2795	5.5	6.8	2795	3,3	5,3
Swollen joints (0–28)	2795	3.5	4.7	2795	1,8	3,2
ESR, mm/h	2795	27.1	22.9	2795	23,5	20,4
CRP, mg/l	2795	15.1	31.8	2795	9,9	22,9
DAS28	2795	4	1.7	2795	3,4	1,5
CDAI	2795	16.7	14	2795	11,1	10,6
SDAI	2795	18.2	15	2795	12,1	11,3
HAQ-DI	1980	1.2	0.7	1879	1.0	0.7

DAS28: 28-joint DAS; CDAI: clinical disease activity index; SDAI: simplified disease activity index; HAQ-DI: Health Assessment Questionnaire Disability Index.

the selected visits are a representative sample of the overall pool of visits, we started by comparing the percentages of visits in each disease activity state, according to DAS28, with the dataset containing all visits (21 471) where it was possible to calculate this score. This comparison revealed an almost identical distribution of visits in the two datasets (differences <2%).

Correlation between indices

Using PCCs, we found a strong correlation between the scores of the three indices in the overall dataset of 14 440 visits: $r = 0.874$ for DAS28/CDAI, $r = 0.877$ for DAS28/SDAI and $r = 0.984$ for CDAI/SDAI (all *P*-values <0.0001).

Cut-off agreement

Each of the 14 440 visits was categorized according to the disease state, applying the cut-offs established for each of the three indices (see supplementary Table S1, available at *Rheumatology* Online). Analysing all four groups of disease activity states simultaneously ($\kappa = 4$), kappa values with quadratic weighting were all >0.8, indicating strong agreement between cut-offs (see supplementary Table S2, available at *Rheumatology* Online). However, the percentage of visits in each disease activity category varied considerably according to the index used. The percentage of visits classified as remission was much higher using the DAS28 and all indices revealed a much higher percentage of visits in remission than the 2011 ACR/EULAR Boolean-based remission criteria [16]: according to these criteria, only 1795 visits (12.43%) could be classified as in remission.

In order to understand these apparent contradictions, we started by performing two other statistical tests (see supplementary Tables S2 and S3, available at *Rheumatology* Online) using the 2×2 contingency tables created as described in Methods. Using kappa statistics ($\kappa = 2$), kappa values >0.8 are only found for CDAI and SDAI agreement. After performing McNemar's chi-squared tests, we concluded that the distribution of visits per disease activity category was highly significantly discordant between the three indices (*P*-values are nearly zero), except when we compared visits in the remission and low disease activity states grouped together.

In order to address the clinical relevance of the discordance between categorical thresholds we calculated PCCs and percentages of non-concordant visits (see Table 2 and supplementary Table S4, available at *Rheumatology* Online) for each disease activity state separately. To this purpose, each visit was classified in a given disease activity state if this was granted by at least one of the two compared indices (*n* Total). Observed disagreement for visits classified as in remission by either DAS28 modified cut-offs or CDAI/SDAI was about 57.1%/54.4%, respectively. Disagreement between DAS28 modified cut-offs and the other indices was still very high (~55%) for low disease activity. It decreased in moderate and high disease activity, still remaining >30%. The percentage of disagreement was much lower between CDAI and SDAI, ranging from 12.8% to 20.4% according to the disease activity state analysed. Although not directly compared, we also present analogous results for the DAS28 original cut-offs. As expected, disagreements were much greater, reaching up to 73.8% for the low disease activity state.

When the visits where the patient was exposed to biologic treatment were compared with the visits where the patient was not exposed to biologic treatment, we found no significant disagreements between the percentages of non-concordant visits in these two subsets, if and only if the low and moderate disease activity states were compared. For remission and high disease activity states, the percentages of non-concordant visits were higher in visits where the patient was exposed to biologic treatment (see supplementary Tables S5–S7, available at *Rheumatology* Online).

When the six centres with >1000 visits were analysed separately, we found high percentages of non-concordant

TABLE 2 Non-concordant visits for disease activity state according to DAS28, CDAI and SDAI disease states and PCCs within disease activity states

Compared indices		Non-concordant visits		Pearson's coefficient	
	N total	*n*	%	*r*	*P*-value
Remission					
DAS28 modified *vs* CDAI	4146	2367	57.09	0.022	0.1541
DAS28 original *vs* CDAI	4718	2693	57.08	0.131	<0.0001
DAS28 modified *vs* SDAI	4104	2231	54.36	0.062	0.0001
DAS28 original *vs* SDAI	4677	2559	54.71	0.168	<0.0001
CDAI *vs* SDAI	2677	412	15.39	0.517	<0.0001
Low					
DAS28 modified *vs* CDAI	7182	3998	55.67	0.348	<0.0001
DAS28 original *vs* CDAI	6444	4756	73.81	0.328	<0.0001
DAS28 modified *vs* SDAI	7036	3839	54.56	0.355	<0.0001
DAS28 original *vs* SDAI	6292	4585	72.87	0.334	<0.0001
CDAI *vs* SDAI	6101	781	12.80	0.824	<0.0001
Moderate					
DAS28 modified *vs* CDAI	5595	2697	48.20	0.521	<0.0001
DAS28 original *vs* CDAI	6312	3383	53.60	0.545	<0.0001
DAS28 modified *vs* SDAI	5714	2536	44.38	0.548	<0.0001
DAS28 original *vs* SDAI	6475	3310	51.12	0.586	<0.0001
CDAI *vs* SDAI	4489	871	19.40	0.830	<0.0001
High					
DAS28 modified *vs* CDAI	2516	936	37.20	0.709	<0.0001
DAS28 original *vs* CDAI	2870	976	34.01	0.716	<0.0001
DAS28 modified *vs* SDAI	2273	768	33.79	0.683	<0.0001
DAS28 original *vs* SDAI	2694	942	34.97	0.716	<0.0001
CDAI *vs* SDAI	2455	500	20.37	0.910	<0.0001

CDAI: clinical disease activity index; SDAI: simplified disease activity index; PCCs: Pearson's correlation coefficients; DAS28 original: 28-joint DAS, original cut-offs; DAS28 modified: 28-joint DAS, modified cut-offs; *r* = PCC value; *N* total: number of visits classified at a given activity level by any of the two scores under comparison.

visits in all of them, although some of these percentages were higher in some centres when compared with the others (see supplementary Table S8, available at *Rheumatology* Online).

Discussion

Nowadays, we have distinct validated instruments to assess disease activity and it is relevant to understand whether they can be used interchangeably. The RA Clinical Disease Activity Measures Working Group of the ACR has recently issued recommendations for clinical practice [21]. Six different disease assessment tools are recommended: DAS28, CDAI, SDAI and three patient-driven tools— Patient Activity Scale (PAS), PAS-II [22] and Routine Assessment of Patient Index Data with three measures (RAPID-3) [23]. However, according to the authors, psychometric properties of the three patient-driven indices indicate that they are less reliable than DAS28, CDAI and SDAI.

Nevertheless, no hierarchy of choice is proposed and the clinical implications of the respective cut-offs are not discussed.

The ACR working group recognizes that there is currently no ideal measure of disease activity and thus cannot recommend a single tool. Furthermore, no choice is explicitly made in recent treatment guidelines and recommendations [21, 24–26].

Our data show that the classification into disease activity categories following currently established cut-offs of DAS28, CDAI and SDAI results in discrepancies that are not only statistically significant, but also highly relevant from the clinical point of view, as they would impact upon therapy decisions in a high percentage of cases. This is particularly relevant when the comparison was established between DAS28 and the other two indices, especially at lower levels of disease activity. The new cut-offs proposed for DAS28 reduced the effect but did not satisfactorily resolve this issue.

Disagreements in the classification of as much as 54% of cases regarding remission stress the need to understand the underlying reasons, despite the fact that CDAI and SDAI were not conceived to replace DAS28. Other authors have also found significant disagreements between these indices and that they should not be applied in clinical practice interchangeably [27]. The importance of all these disagreements and the need to correct or resolve them cannot be overstated when guidelines and recommendations for the treatment of RA are increasingly based on numerical definitions of disease activity level.

Although other authors have reached the same conclusions, we found more disagreements than those previously published. For example, when comparing CDAI and SDAI, disagreement percentages range from ~15% to 20% and the correlation coefficient for remission is only moderate (see Table 2), which may contradict previous conclusions that acute phase reactants add little to composite disease activity indices for RA. The most significant results are presented in Table 2, but several other statistical tests were performed in order to confirm these disagreements. We are aware that with a cross-sectional study design we cannot analyse the evolution of disagreements over time. Nevertheless, the correct statistical approach in measuring agreement is not obvious and methodological errors in the design of agreement studies are identified by several authors [28–34].

In conclusion, it is clear from our data that the cut-offs of the DAS28, SDAI and CDAI frequently assigned different states of disease activity for the same visit. It is mandatory to develop further research devoted to understanding the reasons for disagreement and to establish the best cut-offs to represent the clinical reality and to be associated with the currently proposed therapeutic implications.

Rheumatology key messages

- The current cut-offs of DAS28, SDAI and CDAI correspond to different states of RA disease activity.
- These differences may have considerable implications regarding the application of target-oriented RA treatment recommendations in practice.
- Further research is needed regarding the use of composite scores as guides for RA treatment.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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