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Original article

Correlation of rheumatoid arthritis activity indexes (Disease Activity Score 28 measured with ESR and CRP, Simplified Disease Activity Index and Clinical Disease Activity Index) and agreement of disease activity states with various cut-off points in a Northeastern Brazilian population

Marta Maria das Chagas Medeiros[a,*], *Brenda Maria Gurgel Barreto de Oliveira*[b], *João Victor Medeiros de Cerqueira*[c], *Raquel Telles de Souza Quixadá*[b], *Ídila Mont'Alverne Xavier de Oliveira*[b]

[a] *Faculdade de Medicina, Universidade Federal do Ceará, Fortaleza, CE, Brazil*
[b] *Hospital Universitário Walter Cantídio, Fortaleza, CE, Brazil*
[c] *Universidade de Fortaleza, Fortaleza, CE, Brazil*

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ABSTRACT

Introduction: The Disease Activity Score 28 (DAS28) and its versions have been used to measure rheumatoid arthritis activity, but there is no consensus about which one is the best.
Objectives: Determine the correlation among indexes (DAS28 ESR, DAS28 CRP, SDAI and CDAI) and evaluate agreement of activity strata using different cut-off points.
Methods: Rheumatoid arthritis patients were cross-sectionally evaluated with data collection to calculate the DAS28 (ESR and CRP), SDAI and CDAI, using different cut-offs for defining remission, mild, moderate and high activity. Pearson correlations were calculated for continuous measures and agreement (kappa test) for the strata (remission, mild, moderate and high activity).
Results: Of 111 patients included, 108 were women, age 55.6 years, 11-year disease duration. DAS28 (ESR) was significantly higher than DAS28 (CRP) (4.0 vs. 3.5; $p < 0.001$) and the values remained higher after stratification by age, gender, disease duration, rheumatoid factor and HAQ. Correlations among indexes ranged from 0.84 to 0.99, with better correlation between SDAI and CDAI. Agreements among activity strata ranged from 46.8% to 95.8%. DAS28 (CRP) with cut-off point for the remission of 2.3 underestimated disease activity by 45.8% compared with DAS28 (ESR). SDAI and CDAI showed agreement of 95.8%. The four indexes were associated with disease duration and HAQ.

* *Corresponding author.*
E-mail: mmcmedeiros@hotmail.com (M.M.C. Medeiros).
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Conclusions: Although the activity indexes show good correlation, they show discrepancies in activity strata, thus requiring more researches to define a better index and better cut-off points.

Correlação dos índices de atividade da artrite reumatoide (Disease Activity Score 28 medidos com VHS, PCR, Simplified Disease Activity Index e Clinical Disease Activity Index) e concordância dos estados de atividade da doença com vários pontos de corte numa população do nordeste brasileiro

Palavras-chave:
Artrite reumatoide
Atividade doença
DAS28
Correlação
Concordância

RESUMO

Introdução: O Disease Activity Score 28 (DAS28) e versões têm sido usados para medir atividade da artrite reumatoide (AR), mas não existe consenso sobre qual é o melhor.
Objetivos: Determinar a correlação entre os índices (DAS28 VHS, DAS28 PCR, SDAI e CDAI) e avaliar a concordância dos estratos de atividade com o uso de diferentes pontos de corte.
Métodos: Pacientes com AR foram avaliados transversalmente com coleta de dados para cálculo do DAS28 (VHS e PCR), SDAI e CDAI, com o uso de pontos de cortes diferentes para definição de remissão, atividade leve, moderada e alta. Correlações de Pearson foram calculadas para medidas contínuas e concordância (teste de kappa) para os estratos (remissão, atividade leve, moderada e alta).
Resultados: De 111 pacientes incluídos, 108 foram mulheres, média de 55,6 anos, tempo de doença de 11 anos. DAS28 (VHS) foi significantemente maior do que DAS28 (PCR) (4 vs. 3,5; $p < 0{,}001$) e os valores permaneceram maiores após estratificação por idade, sexo, tempo doença, fator reumatoide e HAQ. Correlações entre índices variaram de 0,84 a 0,99, com melhor correlação entre SDAI e CDAI. Concordâncias entre estratos de atividade variaram de 46,8% a 95,8%. DAS28 (PCR) com ponto de corte para remissão de 2,3 subestimou atividade da doença em 45,8% quando comparado com DAS28 (VHS). SDAI e CDAI apresentaram concordância de 95,8%. Os quatro índices mostraram associação com tempo de doença e HAQ.
Conclusões: Embora os índices de atividade apresentem boa correlação, mostram discrepâncias nos estratos de atividade. Tornam-se necessários mais estudos para definir melhor índice e melhores pontos de corte.

Introduction

The main goals to be achieved during the treatment of patients with rheumatoid arthritis (RA) are pain relief and the strict control of the joint inflammatory process. Aiming at having a more adequate evaluation of the inflammatory activity in clinical trials, the American College of Rheumatology (ACR), the European League Against Rheumatism (EULAR) and the World Health Organization/International League Against Rheumatism (WHO/ILAR) proposed a set of variables (core sets), which included the number of tender and swollen joints, measurement of pain, global assessment of disease activity by the physician and patient, acute phase reactant and functional measure.[1–3]

In the early 90s another index to measure RA activity in clinical practice was proposed, and was called Disease Activity Score (DAS), which considers the number of tender and swollen joints, erythrocyte sedimentation rate (ESR) and assessment performed by the patient of global health or of disease activity.[4] This original DAS uses Ritchie articular index (26 joint regions) to assess the number of painful joints, and 44 joints to evaluate the swollen ones. Later, the proposed DAS28 started using only 28 joints for counting the swollen and tender joints[5] and allowed the optional use of C-reactive Protein (CRP) instead of ESR as an inflammatory marker.[6] Since then, DAS28 was the most common measure used to evaluate the inflammatory activity, both in clinical trials and in clinical practice. However, this index requires a complex formula including square root of Naperian logarithm, requiring a technology tool for its calculation. Therefore, more simple indexes were later proposed: Simplified Disease Activity Index (SDAI)[7] and Clinical Disease Activity Index (CDAI).[8] SDAI is a measure proposed by Smolen et al.,[7] the result of which is the simple sum of the number of painful joints (28 joints), number of swollen joints (28 joints), assessment of disease activity made by the patient in a visual analog scale from 0 to 10 cm, evaluation of disease activity by the physician (0–10 cm) and CRP (mg/dL). The calculation of the CDAI is simpler because the sum does not

Table 1 – Cut-off points of indexes DAS28, SDAI, and CDAI to define states of disease activity.

Indexes	Disease remission	Mild activity	Moderate activity	High activity
Original DAS28 (ESR)[5]	<2.6	2.6–3.2	>3.2–5.1	>5.1
DAS28 (ESR) Aletaha et al.[16]	<2.4	2.4–3.6	>3.6–5.5	>5.5
DAS28 (CRP) Inoue et al.[17]	<2.3	2.3–2.7	>2.7–4.1	>4.1
DAS28 (CRP) Castrejón et al.[18]	<2.3	2.3–3.8	>3.8–4.9	>4.9
DAS28 (CRP) Fujiwara et al.[11]	<1.72	1.72–2.98	>2.98–4.77	>4.77
SDAI[7]	<3.3	3.3–11	>11–26	>26
CDAI[8]	<2.8	2.8–10	>10–22	>22

DAS28, Disease Activity Score (28 joints); SDAI, Simplified Disease Activity Index; CDAI, Clinical Disease Activity Index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

take CRP into account, only the first four measures. Although indexes show good correlation with each other,[7–11] DAS28 is the most validated index for measuring disease activity. Another advantage is that it is possible to use both ESR and CRP as an inflammatory marker, but use of this latter marker still requires further study, since discrepancies between ESR and CRP have been reported in some patients with RA, with a trend toward higher values of ESR and lower values of CRP.[12,13]

All these indexes (DAS28, SDAI and CDAI) measure disease activity on a continuous scale, and also allow categorizing the patient in activity strata, using different cut-off points: remission, mild, moderate and high activity. With the emergence of several new drugs in the last 15 years to treat RA, disease remission is a goal that shall be sought. The indexes cut-off points that define disease remission vary in the literature. For example, the original DAS28 established that clinical remission was defined when DAS28 (ESR) was <2.6.[5] In 2005, Aletaha et al. proposed to lower the cut-off point to <2.4.[14] As to the best cut-off point to define remission when CRP is used in the calculation of DAS28, a value below 2.3 was already suggested.[15,16] In 2013, Fujiwara and Kita's study concluded that the best index to define clinical remission was DAS28 measured by CRP with the conventional cut-off of 2.3 reduced to 1.72.[10] The cut-off points for other activity strata of the disease also vary among the indexes and this can lead to inconsistency in the classification of disease activity, resulting in different practices, also affecting the comparison of studies when using different criteria.

Another very important point is that the possibility of patients' ethnic origin influences the activity indexes, making the generalization of studies' results inadequate. Differences in genetic polymorphism that influences CRP levels, as well as other genetic and cultural factors of each population, can influence disease activity measures, requiring that studies on the subject are developed in different populations to establish the best index. Studies comparing different versions of DAS28 were performed predominantly in Europe and Asia and in some African-American and black African populations.

The objectives of this study were to determine a correlation among the most popular indicators for measuring activity of rheumatoid arthritis (DAS28 calculated with ESR, DAS28 calculated with CRP, SDAI and CDAI) and assess the agreement of disease activity states defined by the indexes using different cut-off points of DAS28 in a sample of patients in northeastern Brazil.

Methods

Patients with RA diagnosis according to ACR criteria[17] who were followed in the outpatient's of the Rheumatology service of the University Hospital Walter Cantidio at the Federal University of Ceará were sequentially invited to participate in the study. The presence of other autoimmune diseases, except secondary Sjogren's syndrome, were excluded. The study design was cross-sectional. Data collection took place from January to December 2013. Demographic data (gender, age, race, education level), clinical data related to RA (disease duration since diagnosis, presence of extra-articular manifestations, rheumatoid factor, medications used), were collected from medical records.

To calculate the activity indexes of the disease (DAS28, SDAI and CDAI), the rheumatologist on the day of consultation collected the following data: count of the number of painful and swollen joints in 28 joints (shoulders, elbows, wrists, metacarpophalangeal, proximal interphalangeal, knees), global health assessment (scale 0–100) by the patient, assessment of disease activity by the patient and physician (0–10) and inflammatory activity markers carried out within a maximum period of 2 weeks before the consultation (ESR and CRP). If the patient's condition had changed after the completion of inflammatory markers, these were not considered and a new assessment was scheduled. Patients with categorical CRP results (positive or negative; < or >) were not considered for calculation of indexes that take CRP into account. Laboratory tests were performed at the Central Laboratory of HUWC and the methods employed were: ESR (Sedi-System Automation) and CRP (immunoturbidimetry ROCHE COBAS). DAS28 was calculated with software for specific calculation of DAS, using both ESR and CRP (mg/dl), global health assessment by the patient, and the number of tender and swollen joints (28 joints). SDAI was calculated by adding the number of swollen joints (0–28), number of tender joints (0–28), evaluation of disease activity by the patient (0–10), evaluation of disease activity by the doctor (0–10) and the value of CRP (0.1–10 mg/dL). The result of the CDAI was the sum of the four previous clinical measurements without CRP.

The cut-off points considered to define the inflammatory activity states are shown in Table 1. For the DAS28 calculated with ESR, we used the cut-off points of the original study[5] and the study of Aletaha et al.[14] For the DAS28 calculated with CRP

we used the cut-off points proposed by Inoue et al.,[15] Castrejon et al.[16] and Fujiwara et al.[10] The physical function was assessed using the Health Assessment Questionnaire (HAQ)[18] with score of 0–3, with 0 score meaning no loss of physical function, 3, full disability.

Statistics

Paired data of continuous variables as DAS28 (ESR) and DAS28 (CRP) and SDAI and CDAI were compared using paired *t*-test. To estimate correlation between the continuous values of DAS28 (ESR), DAS28 (CRP), SDAI, CDAI and HAQ Pearson's correlation coefficient was used. To compare the averages, Kruskal Wallis and Mann Whitney tests were used. The agreement between the inflammatory activity states (remission, mild, moderate and high activity) was determined by kappa test. The level of statistical significance was 0.05. Statistical analysis was performed using STATA version 9.0 software.

Results

A total of 111 patients were studied, predominantly female (108 women and 3 men), most of them of white/brown race (62%) with a mean age of 55.5 years (SD = 12.9) and duration of disease of 11.08 years (SD = 7.3) (Table 2). Rheumatoid factor was positive in 84.1% of the sample and most made use of methotrexate and/or leflunomide (95.5% and 71.2%). The mean (± SD) and median (interquartile range 25–75) values of DAS28 (ESR), DAS28 (CRP), SDAI, CDAI and HAQ are also shown in Table 2. Mean DAS28 (ESR) was statistically higher than mean DAS28 (CRP) ($p < 0.001$) and also that of SDAI was statistically higher than CDAI ($p < 0.001$). The calculation of the indexes using CRP was done with 96 of the 111 patients because 15 patients did not get the proper dosage of CRP, only of ESR.

The mean DAS28 (ESR), DAS28 (CRP), SDAI and CDAI were also evaluated by age strata (<40, 40 to <50, 50 to <60 and ≥60 years), disease duration (≤5, >5–10, >10–20, >20 years), gender, rheumatoid factor (positive, negative), and HAQ (0–1, >1–2, >2–3) (Table 3). The values of the four activity indexes were statistically different for each stratum of disease duration, with the highest values after 20 years of disease, and then with ≤5 years of disease. The average values were also significantly different for HAQ stratum, with progressively increasing values as HAQ score range increased.

Correlations between DAS28 (ESR), DAS28 (CRP), SDAI and CDAI were all statistically significant ($p < 0.0001$). Very strong correlations (>0.90) were observed among DAS28 (ESR) and DAS28 (CRP) (0.92), DAS28 (CRP) and SDAI (0.93), DAS28 (CRP) and CDAI (0.92) and between SDAI and CDAI (0.99). Strong correlations (between 0.6 and 0.9) were observed when comparing DAS28 (ESR) with SDAI and CDAI (0.84). Regular correlations (0.3–0.6) were observed comparing HAQ with DAS28 (ESR) (0.50), DAS28 (CRP) (0.48), SDAI and CDAI (both 0.53).

When indexes were categorized by activity strata of the disease (remission, mild, moderate and high activity), the

Table 2 – Characteristics of patients with rheumatoid arthritis.

Characteristics	
Female (%)	97.3%
Age (mean ± SD)	55.6 ± 12.9
Skin color (%)	
White	22.2%
Brown	31.5%
Brunette	39.8%
Black	6.5%
Marital Status (%)	
Single	33.9%
Married	50.5%
Separated/widower	15.6%
Education level (%)	
Illiterate/literate	33.6%
1st Grade	40.0%
2nd Grade	22.7%
Graduation	3.7%
Disease duration (years)	
Mean ± SD	11.08 ± 7.3
Median (interquartile range)	10 (5.16)
Rheumatoid factor (%)	84.1%
Medications used (%)	
Chloroquine	58.6%
Methotrexate	95.5%
Leflunomide	71.2%
Sulfasalazine	15.3%
Biological (anti TNF-α and abatacept)	22.5%
Current daily dose of prednisone (mg)	
Mean ± SD	5.1 ± 2.2
ESR (mm/h)	
Mean ± SD	29.7 ± 21.5
Median (interquartile range)	24.5 (15–38)
CRP (mg/dL)	
Mean ± SD	0.9 ± 1.0
Median (interquartile range)	0.6 (0.3–1.1)
DAS28 (ESR)	
Mean ± SD	4.03 ± 1.40
Median (IQ)	3.99 (3.09–4.92)
DAS28 (CRP)	
Mean ± SD	3.55 ± 1.27
Median (IQ)	3.38 (2.52–4.47)
SDAI	
Mean ± SD	16.53 ± 10.54
Median (IQ)	14.1 (9.05–22.4)
CDAI	
Mean ± SD	15.62 ± 10.03
Median (IQ)	13.5 (8–21)
HAQ	
Mean ± SD	0.98 ± 0.69
Median (IQ)	1 (0.37–1.62)

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; DAS28 (ESR), disease activity score using ESR; DAS28 (CRP), disease activity score using CRP; SDAI, Simplified Disease Activity Index; CDAI, Clinical Disease Activity Index; HAQ, health assessment questionnaire.
Comparing DAS28 (ESR) with DAS28 (CRP) and SDAI with CDAI, the level of statistical significance was <0.001.

Table 3 – Values (median ± SD) of DAS28 (ESR), DAS28 (CRP), CDAI and SDAI by strata of age, disease time, rheumatoid factor and sex.

	DAS28 (ESR) (*n* = 111)	DAS28 (CRP) (*n* = 96)	SDAI (*n* = 96)	CDAI (*n* = 111)
Age:				
<40 years	3.7 ± 1.6	3.6 ± 1.3	14.9 ± 11.0	14.4 ± 11.0
40–49 years	3.8 ± 1.4	3.6 ± 1.3	16.0 ± 10.5	15.2 ± 10.1
50–59 years	4.3 ± 1.3	3.8 ± 1.3	17.8 ± 10.7	16.8 ± 10.1
≥60 years	3.8 ± 1.4	3.3 ± 1.2	13.8 ± 9.3	13.0 ± 8.9
p	NS	NS	NS	NS
Gender:				
Female	3.9 ± 1.3	3.5 ± 1.3	15.5 ± 10.0	14.7 ± 9.6
Male	5.0 ± 2.3	5.1 ± 0.6	24.6 ± 17.5	22.6 ± 15.0
p	NS	0.07	NS	NS
Disease time:				
≤5 years	4.4 ± 1.4	4.1 ± 1.2	20.2 ± 10.7	19.0 ± 10.2
>5–10 years	3.7 ± 1.3	3.4 ± 1.2	13.9 ± 10.1	13.0 ± 9.7
>10–20 years	3.6 ± 1.3	3.1 ± 1.2	12.7 ± 9.2	12.1 ± 8.7
>20 years	5.0 ± 1.2	4.2 ± 0.8	22.8 ± 5.7	22.0 ± 5.6
p	0.007	0.003	0.0005	0.0005
Rheumatoid factor:				
Positive	3.9 ± 1.3	3.6 ± 1.2	15.7 ± 9.6	14.9 ± 9.3
Negative	3.9 ± 1.7	3.5 ± 1.6	16.6 ± 14.0	15.6 ± 13.2
p	NS	NS	NS	NS
HAQ:				
0–1	3.5 ± 1.2	3.1 ± 1.1	11.8 ± 8.4	11.2 ± 8.1
>1–2	4.5 ± 1.4	4.0 ± 1.3	20.8 ± 10.3	19.8 ± 9.8
>2–3	4.7 ± 1.6	4.2 ± 1.2	23.0 ± 9.7	21.6 ± 8.9
p	0.001	0.001	0.0001	0.0001

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; DAS28 (ESR), disease activity score using ESR; DAS28 (CRP), disease activity score using CRP; SDAI, Simplified Disease Activity Index; CDAI, Clinical Disease Activity Index; HAQ, health assessment questionnaire.

proportions of patients in each category according to the cut-off points adopted to calculate DAS28 using ESR (original[5] and Aletaha[14]), of DAS28 using CRP (Inoue,[15] Castrejón[16] and Fujiwara[10]) and SDAI and CDAI are presented in Table 4. Reducing the cut-off point from 2.6 to 2.4 in the calculation of DAS28 (ESR) proposed by Aletaha reduces the percentage of patients considered to be in remission from 15.6% to 13.5%. Calculating the DAS28 with CRP and cut-off of 2.3 proposed by Inoue and Castrejon, the percentage of patients in remission categorized as in remission increases about 2.1% and 4.2% compared to original DAS28 criteria (ESR) and Aletaha, respectively (Table 4). The reduction of the cut-off to 1.72 proposed by Fujiwara makes this criterion more stringent for considering remission because it reduces from 15.6% (DAS28 ESR) to 6.3% in this category. Of all the indexes were analyzed and presented in Table 4, the cut-off points of SDAI and CDAI to define clinical remission are the most stringent, reducing from 15.6% through original DAS28 (ESR) calculation to 4.2%. The absence of CRP in the calculation of CDAI does not change anything at all in terms of remission criteria when compared to the SDAI. The percentage of patients in the categories of mild and moderate activity has greater variation among indexes than categories at the extremes (remission and high activity).

The agreements among activity strata (remission, mild, moderate and high activity) of different indexes and on using different cut-off points are shown in Table 5. The best agreement of categories observed was between SDAI and CDAI (95.8%). Only one patient was in a lower category when CDAI definition was used. When original DAS28 (ESR) was compared with the original DAS28 (ESR) proposed by Aletaha, agreement of activity strata was observed in 83.3% of patients (80/96) with 14 patients (14.6%) falling to a lower category (underestimated activity) when using Aletaha criteria (Table 6). When original DAS28 (ESR) was compared with DAS28 (CRP) by Inoue, Castrejon and Fujiwara, the best agreement was with Fujiwara criteria (67.7%). The cut-off points suggested by Castrejón underestimated the activity in almost half of the patients (45.8%), while those by Inoue and Fujiwara underestimated by 16.6%. The proportions of overestimated categories by Castrejon, Inoue and Fujiwara were, respectively, 7.3%, 20.8% and 14.6%. Comparing indexes that use CRP to calculate the DAS28, the best agreement was that between what was proposed by Inoue and Fujiwara (71.8%), with Fujiwara overestimating the strata in 11 patients (11.4%) and underestimating in 16 patients (16.7%). The other agreements between multiple comparisons performed ranged from 46.8% to 67.7%.

Discussion

With the growing and urgent need for assessment of rheumatoid arthritis activity not only in clinical practice but also in the evaluation of efficacy of new treatments in clinical trials, it is increasingly important to have instruments to measure disease activity as accurately as possible. Some indexes have been proposed in recent decades; however, they still have properties that need better validation, since they were tested in specific populations.[4–16] There are two main ways to compare the rates between them: (1) as continuous measures, comparing means and medians in the same patients and (2) as categorical measures (remission, mild, moderate and high activity) and comparing the agreement among strata.

In the present study, we analyzed DAS28 calculated with ESR and CRP, SDAI and CDAI as continuous variables, and also compared the four strata to each other according to the criteria originally proposed[5] and more recently by Aletaha[14] for the calculation of DAS28 using ESR; the criteria were proposed for DAS28 using CRP according to three studies (Inoue,[15] Castrejón[16] and Fujiwara[10]) and SDAI and CDAI. The first observation in this study, corroborated by several other studies,[8,13,16,19–21] is that the values of DAS28 with ESR are higher than the values of DAS28 by CRP, even when stratified by age groups, disease duration, rheumatoid factor, gender and HAQ score. Therefore, the activity of the disease may be underestimated when using DAS28 with CRP instead of DAS28 with ESR. The excellent correlation between the indexes observed in our study was also registered by other authors.[13,15,21–23] Although the correlation between the two indexes has been very high (92%), the correlation in the four activity strata comparing the original DAS28 (ESR) with DAS28 (CRP) with different cut-off points

Table 4 – Proportion of patients in remission, mild, moderate and high activity according to the scores of DAS28 (ESR), DAS28 (CRP), SDAI and CDAI.

	Remission	Mild activity	Moderate activity	High activity
Original DAS28 (ESR)	15.6%	12.5%	50.0%	22.9%
DAS28 (ESR) Aletaha et al.	13.5%	28.1%	36.5%	21.9%
DAS28 (CRP) Inoue et al.	17.7%	13.5%	37.5%	31.3%
DAS28 (CRP) Castrejón et al.	17.7%	43.7%	21.9%	16.7%
DAS28 (CRP) Fujiwara et al.	6.3%	30.2%	43.7%	19.8%
SDAI	4.2%	30.2%	48.9%	16.7%
CDAI	4.2%	31.3%	44.8%	19.7%

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; DAS28 (ESR), disease activity score using ESR; DAS28 (CRP), disease activity score using CRP; SDAI, Simplified Disease Activity Index; CDAI, Clinical Disease Activity Index.

Table 5 – Proportions of agreement and kappa coefficients among DAS28 (ESR), DAS28 (CRP), SDAI, and CDAI by strata of disease activity.

	Kappa coefficient	Agreement
Original DAS28 (ESR) vs. DAS28 (ESR) Aletaha	0.76	83.3%
Original DAS28 (ESR) vs. DAS28 (CRP) Inoue	0.46	62.5%
DAS28 (ESR) original vs. DAS28 (CRP) Castrejón	0.31	46.8%
Original DAS28 (ESR) vs. DAS28 (CRP) Fujiwara	0.53	67.7%
Original DAS28 (ESR) vs. SDAI	0.46	63.5%
Original DAS28 (ESR) vs. CDAI	0.44	61.5%
DAS28 (CRP) Inoue vs. DAS28 (CRP) Castrejón	0.42	55.2%
DAS28 (CRP) Inoue vs. DAS28 (CRP) Fujiwara	0.61	71.8%
DAS28 (CRP) Inoue vs. SDAI	0.38	56.2%
DAS28 (CRP) Inoue vs. CDAI	0.42	58.3%
DAS28 (CRP) Castrejón vs. DAS28 (CRP) Fujiwara	0.45	60.4%
DAS28 (CRP) Castrejón vs. SDAI	0.38	55.2%
DAS28 (CRP) Castrejón vs. CDAI	0.35	53.1%
SDAI vs. CDAI	0.93	95.8%

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; DAS28 (ESR), disease activity score using ESR; DAS28 (CRP), disease activity score using CRP; SDAI, Simplified Disease Activity Index; CDAI, Clinical Disease Activity Index.

ranged from 46.8% to 62, 5% of patients. Therefore, an excellent correlation does not necessarily mean good agreement between the categories of activity. For instance, the criteria proposed by Castrejón et al. underestimate the level of activity in almost half of the patients. The study by Tamhane et al., comparing original DAS28 (ESR) with DAS28 (CRP) by Inoue and Castrejon, also found an underestimation of disease activity in 40% of patients when the CRP was used.[13] This can be explained by lowering of the cut-off point and expansion of the range of mild activity and reduction of the cut-off for high activity, causing a greater number of patients to migrate from higher categories to lower ones. Importantly, Castrejón et al.[16] estimated these cut-off points in a population of patients with recent-onset RA (median duration of disease in the first visit: 6 months; IQ 3.6–9 months). The population tested in this study was of patients with long-term RA (mean: 11.08 ± 7.3 years; median: 10 years; IQ: 5–16 years) and the study by Tamhane et al.[13] had an average of 6.6 ± 9.3 years (median: 1.8 years; IQ: 0.8–9.3). When we categorize the time of disease in groups (≤5 years, >5–10 years;

Table 6 – Agreement between original DAS28 (ESR) and DAS28 (ESR) by Aletaha et al.

	Remission (Aletaha)	Mild activity (Aletaha)	Moderate activity (Aletaha)	High activity (Aletaha)	Total patients
Remission (original)	13	2	0	0	15
Mild activity (original)	0	12	0	0	12
Moderate activity (original)	0	13	34	0	47
High activity (original)	0	0	1	21	22
Total	13	27	35	21	96

ESR, erythrocyte sedimentation rate; DAS28 (ESR), disease activity score using ESR.

>10–20 years and >20 years) the average values of all evaluated indexes were statistically different, with the highest values at the extremes of age. We can conclude that the duration of disease can influence the disease activity indexes and therefore validation of a particular index should take the time of the disease into consideration. The cut-off points proposed by Castrejon et al.[16] may not apply to patients with long-term disease. The cut-offs of DAS28 (CRP) by Inoue and Fujiwara were established in a population of patients with long-standing RA (about 10 years) and both underestimated the level of activity in only 16.6% when compared with original DAS28 (ESR), and overestimated in 20.8% and 14.6%, respectively. Analyzing these properties, it appears that the reduction of all cut-off points for the four strata proposed by Fujiwara is closer to the original DAS28 criteria (ESR).

SDAI and CDAI correlated with DAS28 (ESR) of 0.84, and the first two with each other of 0.99. In the original study of SDAI the correlation with DAS28 (ESR) was 0.90.[7] Statistical validity excluding CRP from SDAI was very much tested in the original study of CDAI.[8] In several analyses made between SDAI and CDAI, the values correlated almost perfectly and the correlations between SDAI or CDAI with original DAS28 (ESR) ranged from 0.87 to 0.90. Although CRP showed no significant colinearity with other SDAI measures, only 5% of the SDAI remained unexplained when it excluded CRP; in DAS28 (ESR), ESR only contributed to about 15%. Mean CDAI values are obviously smaller than the SDAI, since the value of CRP is suppressed in the calculation. The degrees of agreement of this study of original DAS28 (ESR) with the original SDAI and CDAI were low, but the agreement of SDAI with CDAI was almost perfect (95.8%). This high agreement reinforces that the exclusion of CRP for the calculation of CDAI almost does not change anything in the assessment of disease activity level compared to SDAI. Only 4 of the 96 patients analyzed disagreed regarding the stratum.

Defining a patient as in remission can mean reduction or even withdrawal of some drugs in use and, therefore, the criteria shall prevent that a patient with residual activity ceases to be properly treated (underestimation of activity), and shall also prevent the patient from being overtreated (activity overestimation). The definition of high activity is important, especially for defining the introduction of biological agents, and also for prognostic reasons, since the probability of more rapid progression is greater in patients that keep the highest activity. The categorization of high disease activity levels is also an important factor for eligibility of patients in clinical trials. Comparing the rates tested in this study, the most rigorous for the category of remission are SDAI and CDAI. While 15.6% of the patients studied were classified in this stratum by original DAS28 (ESR), only 4.2% were at this level by SDAI and CDAI. The cut-off point used by Fujiwara for the remission of 1.72, well below the cut-off points of the other indexes, classified 6.3% of patients as in remission. Regarding the definition of high activity, the index covering more patients in this stratum was DAS28 (CRP) by Inoue (31.3%) and the lowest number was SDAI and DAS28 (CRP) by Castrejon (16.7%). So, for the definition of high activity, DAS28 (CRP) by Inoue was the most sensitive in the population tested in this study.

Another interesting finding of this study is that the mean values of the four indexes studied increased progressively with the increase of HAQ and were statistically different. This can be explained because the physical function can influence the global health assessment and activity made by the patient and doctor. The HAQ correlations with indexes were very similar to other studies.[7,9,14] Age, sex and rheumatoid factor did not influence the values of the indexes studied in the present study. Although the mean values of the four indexes were all numerically higher in men than in women, just for DAS28 (CRP) there was a trend toward statistical difference ($p = 0.07$). The small number of male patients may have influenced the statistical outcome. Some authors suggest that the calculation of DAS28 considers the gender and age,[13,21] but this has not been established and validated.

In short, while the indexes DAS28 (ESR), DAS28 (CRP), SDAI and CDAI correlated well with each other, they had many discrepancies regarding the categories/strata of inflammatory activity. Regarding the calculation of DAS28, the value of disease activity as measured using CRP was underestimated compared to the measure using ESR. Therefore, the definition of remission and activity by a particular index may not have the same meaning when measured by another index.

The activity of the disease evaluated by SDAI and CDAI showed excellent correlation and agreement, stressing that the CRP dosage is not indispensable for activity clinical assessment. Therefore, CDAI can be used instead of SDAI because its simplicity allows its use at any time, and anywhere. Another interesting fact is that all the indexes evaluated in the study to measure RA activity were associated with disease duration and functional capacity, factors that should be taken into account in the assessment of disease activity as measured by the indexes studied.

The study has some limitations: small sample size, different evaluators to count number of tender and swollen joints, and patients' cultural and ethnic background. A larger sample size would lead to more patients in the four strata of activity according to the cut-off points analyzed, which would increase the power of conclusion of the study. The count of painful and swollen joints may show little variability when made by different evaluators. Ideally, all patients should be always examined by the same observer, or the examination technique should be standardized by the evaluators and trained previously. Patients in the study were from a public institution of tertiary care, with low socioeconomic status, low education and long-standing disease, characteristics that may influence the degree of response of the components to calculate the activity indexes, including the assessment of health and activity status made by patients and counting of painful joints.

Therefore, further studies are needed to establish the best measure of disease activity, and finer cut-off points, so that the indexes more accurately express the inflammatory condition, and the results of the studies are comparable, taking demographic, cultural and clinical factors into account that

may interfere with the assessment of disease activity. Meanwhile, the choice of index to be used will depend on: the objective of assessment (whether for use in daily practice or in clinical trials), the desired goal (remission or therapeutic change), the practice context (availability of technology, laboratory tests, time) and personal clinician preferences. When analyzing published studies, we should consider which index and which cut-off point were used for comparison. In clinical practice, the same index with the same components for calculation should always be consistently used to allow longitudinal comparisons in decision-making.

Conflicts of interest

The authors declare no conflicts of interest.

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