Comparison between DAS28-ESR and DAS28-CRPus for patients with rheumatoid arthritis: application in a population of southern Brazil

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The Disease Activity Score 28 (DAS28) shows discrepancies when using erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) scores to assess rheumatoid arthritis (RA). This study aimed to verify the agreement between the DAS28-CRP and DAS28-ESR scores in patients with RA from the south of Brazil. A unicentric cross-sectional study was performed (n = 56). The diagnosis of the patients followed the American College of Rheumatology/ European League Against Rheumatism criteria, and their DAS28 were calculated. The DAS28-ESR score was higher than the DAS28-CRP (DAS28-ESR mean 4.8±1.6; DAS28-CRP mean 4.3±1.4) for 83.9% of the patients. The DAS28-CRP and DAS28-ESR scores showed a very strong correlation (Pearson's coefficient = 0.922; P<0.0001, 95% CI +0.87 to +0.95, statistical power 100%). Spearman's correlation coefficient (0.49; P=0.0001, 95% CI +0.25 to +0.67, statistical power 47.54%) showed a moderate correlation between the unique components of the DAS28 formulas. There was agreement between the tests in only 36 of the patients (64.29%). Among the discordant categories, DAS28-ESR overestimated the classification in 16 patients (28.5%). The Kappa coefficient between the categories was 0.465 (SE 0.084, 95% CI +0.301 to +0.630), showing a moderate degree of agreement between the instruments. Although the DAS28-ESR and DAS28-CRP were highly correlated, they differed significantly in terms of patient categorization and should not be used interchangeably.

Keywords: Rheumatoid arthritis. C-reactive protein. Erythrocyte sedimentation rate. Remission induction. Disease activity Score 28.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by multiple joint involvement; it can alternate between phases of active inflammation and remission. This inflammation can progress to severe joint damage, deformities, and varying degrees of functional disability.

The primary goal of treating RA is to achieve the state of clinical remission. More broadly, the treatment aims to maximize the long-term quality of life by controlling symptoms, preventing structural damage, and normalizing function (Smolen *et al*., 2016). In aiming to control this disease, measures of disease activity should be obtained and documented regularly in order to promote adjustments in drug therapy (at least every three months) until the desired target is achieved (Smolen *et al*., 2016).

The Disease Activity Score 28 (DAS28) is one of the indexes recommended by the American College of Rheumatology (ACR) to assess disease activity (Anderson *et al*., 2012). This has been widely used in clinical practice

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(Anderson *et al.*, 2012; Felson *et al.*, 2011; Medeiros *et al.*, 2015; Sheehy *et al.*, 2014; Siemons *et al.*, 2014; Son *et al.*, 2016; Wells *et al.*, 2009). The DAS28 is calculated using the following four components: number of tender joints; number of swollen joints; patient's global health score - measured by visual analogue scale (VAS) -; and erythrocyte sedimentation rate (ESR). As an alternative to the ESR, the serum C-reactive protein (CRP) dosage may be used. The ESR reflects disease activity in the preceding weeks and is influenced by factors such as age, gender, fibrinogen levels, hypergammaglobulinemia, rheumatoid factor levels and anemia (Matsui *et al.*, 2007; Son *et al.*, 2016). CRP levels reflect short-term changes (Sengul *et al.*, 2015) and are not influenced by the aforementioned factors, being more sensitive to changes in disease activity (Eissa, El Shafey, Hammad, 2017).

While ESR and CRP values vary according to underlying pathophysiological processes, DAS28-CRP threshold values can be expected to differ from those of DAS28-ESR (Inoue *et al.*, 2007). In addition, the influence of the ethnic origin of patients on the activity indices has been questioned. Medeiros *et al.* (2015) state that genetic polymorphism interferes with CRP levels, as well as other genetic and cultural factors in each population. Thus, studies of different populations are required to verify the accuracy of the test (Medeiros *et al.*, 2015).

Some authors have evaluated the validity of the DAS28-CRP and its cutoff values as a diagnostic measure (Park *et al.*, 2012). The DAS28-CRP has been used with the same cutoff values originally proposed for the DAS28-ESR to determine disease activity. However, recent data have shown a discrepancy between the results of the DAS28-ESR and DAS28-CRP in their determination of disease activity (Castrejón *et al.*, 2008; Matsui *et al.*, 2007; Sengul *et al.*, 2015; Siemons *et al.*, 2014; Son *et al.*, 2016). Applying the same threshold values for the DAS28-ESR and DAS28-CRP may lead to a partially incorrect determination of disease activity and, consequently, may lead to erroneous treatment decisions. In addition, it has been proven that it is essential to assess whether the two methods are in fact interchangeable (Son *et al.*, 2016).

Considering the lack of studies comparing the indices of assessment of RA in the Brazilian population, this study contributes to the local database and to a comparison of data between the international and national literature regarding this issue. To date, there has only been one study by Medeiros *et al.* (2015) in relation to this subject. Several authors have indicated the influence of ethnicity (Eissa, El Shafey, Hammad, 2017; Inoue *et al.*, 2007; Medeiros *et al.*, 2015; Son *et al.*, 2016) on inflammatory markers used to calculate the DAS28, among the various influencing factors. The validation of these instruments for a specific population is extremely important in order to analyze their clinical implication in the evaluation of rheumatoid arthritis. Thus, it is essential to carry out studies that reflect the characteristics of the population studied in our research and to verify if the results of other studies can be reproduced in our population.

The main objective of this study was to investigate the degree of agreement between the DAS28-CRP and DAS28-ESR in residents of southern Brazil with RA, as well as the implications this has for categorizing patients regarding disease activity.

MATERIAL AND METHODS

Study design and ethics

This unicentric cross-sectional study was approved by the local ethics committee according to protocol 2.932.709. All the participants signed an informed consent form (ICF). The inclusion of patients was performed during consultations in the rheumatology clinic at the Regional University Hospital of Campos Gerais - Wallace Thadeu de Mello and Silva (HURCG), in Ponta Grossa Paraná, Brazil. The participants were referred to the Laboratory of Clinical Analyses of the State University of Ponta Grossa to perform the laboratory tests.

All the patients who attended consultations at the rheumatology clinic were submitted to clinical evaluation and had their medical records analyzed. Those classified as having RA according to the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria of 2010 (Aletaha *et al.*, 2010), who agreed to participate and signed the ICF were included in the study. Table I shows the diagnostic criteria for RA, in accordance with Aletaha *et al.*, 2010. Patients who could not attend the blood tests in the lab were excluded.

For both methods, disease activity was classified according to the following cutoff values: high (> 5.1); moderate (≥3.2 to ≤5.1); low (≥2.6 to <3.2); and remission (<2.6), as stated by Anderson *et al.* (2012) according to the American College of Rheumatology recommendations.

TABLE I - The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis

	Score
Classification criteria for RA (score-based algorithm: add score of categories A–D; a score of ≥ 6/10 is needed for classification of a patient as having definite RA)‡	
A. Joint involvement §	
1 large joint ¶	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)**	5
B. Serology (at least 1 test result is needed for classification)††	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)‡‡	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
D. Duration of symptoms§§	
<6 weeks	0
≥6 weeks	1

‡ Although patients with a score of <6/10 are not classifiable as having RA, their status can be reassessed and the criteria might be fulfilled cumulatively over time.

§ Joint involvement refers to any swollen or tender joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are excluded from assessment. Categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement.

¶ "Large joints" refers to shoulders, elbows, hips, knees, and ankles. "Small joints" refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

** In this category, at least 1 of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (e.g., temporomandibular, acromioclavicular, sternoclavicular, etc.).

†† Negative refers to IU values that are less than or equal to the upper limit of normal (ULN) for the laboratory and assay; low-positive refers to IU values that are higher than the ULN but ≤3 times the ULN for the laboratory and assay; high-positive refers to IU values that are >3 times the ULN for the laboratory and assay. Where rheumatoid factor (RF) information is only available as positive or negative, a positive result should be scored as low-positive for RF. ACPA = anticitrullinated protein antibody.

‡‡ Normal/abnormal is determined by local laboratory standards. CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

§§ Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (e.g., pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status.

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Variables analyzed

Patients who attended the laboratory underwent clinical examination to identify tender and/or swollen joints in 28 joints (shoulders, elbows, wrists, metacarpophalangeal, proximal interphalangeal, knees) and were questioned about their overall evaluation of health through a visual analogue scale (VAS). The demographic, clinical and laboratory data were also recorded at that time.

The erythrocyte sedimentation rate was obtained by the Westergren technique, and the C-reactive protein dosage was obtained by the immunoturbidimetric method using Wiener® ultra-sensitive latex (CRP-*us*).

The DAS28-CRP and DAS28-ESR scores were calculated using the following formulas:

$$DAS28\text{-}CRP = 0.56*\sqrt{(TENDER)} + 0.28*\sqrt{(SWOLLEN)} + 0.36*\log(CRP + 1) + 0.014*VAS + 0.96$$

$$DAS28\text{-}ESR = 0.56*\sqrt{(TENDER)} + 0.28*\sqrt{(SWOLLEN)} + 0.7*\log(ESR) + 0.014*VAS$$

(TENDER: tender joint count in 28 joints; SWOLLEN: swollen joint count in 28 joints; VAS: scoring on the visual analogue scale reported by the patient on their overall health assessment, on a scale of 0-100).

Statistical analysis

For the purposes of sample calculation, and considering an I-type error of up to 5%, a statistical power of 80% (type-II error of 20%), and a correlation between scores greater than 0.4, we estimated that approximately 46 patients were required for this study.

The Kolmogorov-Smirnov test was used to verify the normality of distributions. The quantitative data of normal distribution were expressed as mean and standard deviation, while the non-normal distribution data were expressed as median and amplitude. The qualitative variables were demonstrated in absolute number and percentage.

Student's t-test was used to compare the DAS28-CRP and DAS28-ESR averages.

The relationship between the DAS28-ESR and DAS28-CRP, and between its unique components (CRP and ESR), were analyzed using Pearson's correlation coefficient for samples whose distribution followed normality, and by Spearman's coefficient for those that did not present a normal distribution (1 being a perfect correlation; 0.75 to 0.99 very strong; 0.6 to 0.74 strong; 0.3 to 0.59 moderate; 0.1 to 0.29 weak; 0.01 to 0.09 negligible; and 0 indicated no correlation).

For the analysis of the DAS28-CRP and DAS28-ESR measurements and disease classifications, the Kappa correlation coefficient (κ) was used, which is an index that measures the agreement between the evaluations of two instruments when both are classifying the same object (0 to 0.19 represents poor agreement; 0.2 to 0.39 discrete; 0.4 to 0.59 moderate; 0.6 to 0.79 strong; and 0.8 to 1 almost perfect).

The analyses were performed using the GraphPad Prism version 8.0.2 software. The level of statistical significance was lower than 0.05.

RESULTS AND DISCUSSION

Fifty-six patients participated in the study; there was a predominance of females (87.5%), with a mean age of 52.59 (SD ± 11.69) and median disease duration of five years (0.08-40). The demographic, clinical and laboratory characteristics of the 56 analyzed patients are set out in Table II.

TABLE II - Characteristics of the patients (n = 56 patients)

Age (years)[§]	**52.59 ± 11.69**
Female[φ]	49 (87.50)
Disease duration (months)[ι]	60 (1-480)
FR-positive[φ]	39 (69.64)
FR- (IU/ mL)[ι]	64 (0-2048)
TENDER[ι]	5 (0-28)
SWOLLEN[ι]	5 (0-18)

(continues on the next page...)

TABLE II - Characteristics of the patients (n = 56 patients)

Age (years)[§]	**52.59 ± 11.69**
Visual Analog Scale (0-100)[1]	60 (0-100)
CRP (mg/ dL)[1]	3.55 (0-66.3)
ESR (mm/ hr)[1]	24.5 (1-105)
DAS28-CRP[§]	4.3 ± 1.4
DAS28-ESR[§]	4.8 ± 1.6

FR-positive - positive rheumatoid factor; TENDER - number of tender joints; SWOLLEN - number of swollen joints; ESR - erythrocyte sedimentation rate; CRP - serum C-reactive protein dosage; DAS28-CRP - DAS28 using CRP; DAS28-ESR - DAS28 using ESR. [§]Average± standard deviation; [φ]number (%); [1]median (amplitude).

The proportion of positivity for the rheumatoid factor was 69.64%. These had a median of 5 tender joints (0-28) and 5 swollen joints (0-18). The median for VAS was 60 (0-100). The median erythrocyte sedimentation rate was 24.5 mm in the first hour (1-105) and that of the CRP dosage was 3.55 mg / dl (0-66.3).

The mean and standard deviations of the DAS28-ESR and DAS28-CRP were 4.8 ± 1.6 and 4.3 ± 1.4, respectively. In 83.9% of patients the DAS28-ESR was higher than the DAS28-CRP. The two-tailed Student's t-test showed that the mean of the DAS28-ESR was significantly higher than the mean of the DAS28-CRP (P <0.001), with a mean difference of 0.54 (SD ± 0.62, SEM 0.08, 95% CI +0.38 to +0.71).

The DAS28-CRP and DAS28-ESR scores showed a very strong correlation, with a Pearson's correlation coefficient of 0.922 (P <0.0001, 95% CI +0.87 to +0.95, statistical power 100%). The scatter plot showed that almost all the patients had different DAS28-CRP and DAS28-ESR values (Figure 1).
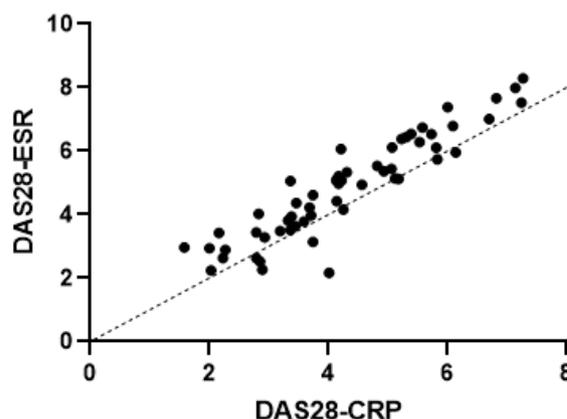

FIGURE 1 - DAS28-ESR (x-axis) scores opposed to DAS28-CRP scores (y-axis). Each point corresponds to a single patient. The diagonal line indicates perfect agreement between the two DAS28 scores.

Spearman's correlation coefficient showed a moderate correlation between the unique components of the DAS28-CRP (0.36 * ln (CRP + 1) + 0.96) and DAS28-ESR (0.7 * ln (ESR)), with a value of 0.49 (P=0.0001, 95% CI +0.25 to +0.67, statistical power 47.54%). The scatter plot showed a large discrepancy between the CPR and ESR component values of the formulas for the same patient (Figure 2).
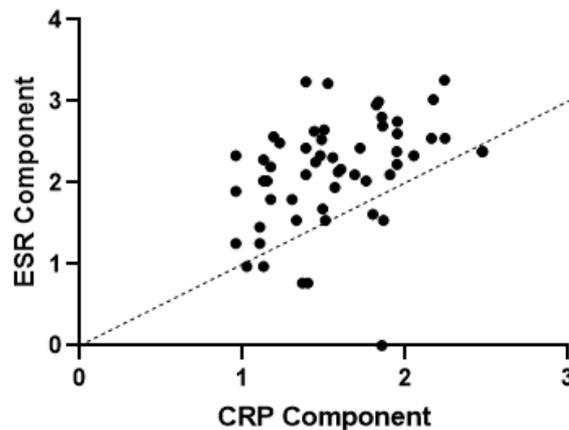

FIGURE 2 - The ESR components of the DAS28-ESR (x-axis) opposed to the CRP components of the DAS28-CRP (y-axis). Each point corresponds to a single patient. The diagonal line indicates agreement between the components.

Table III shows a comparison of the disease activity classifications according to the DAS28-CRP and DAS28-ESR scores calculated for all the studied patients. There was agreement between the tests in only 36 of the patients (64.29%). Some patients were classified into different categories using either formula. Among the discordant categories, the DAS28-ESR overestimated the classification in 16 patients (28.5%), i.e. it classified them in a higher activity category than the DAS28-CRP. The Kappa coefficient between the categories was 0.465 (SE 0.084, 95% CI +0.301 to +0.630), showing a moderate degree of agreement between the instruments and statistical significance.

TABLE III - Comparison of rheumatoid arthritis disease activity using DAS28-CRP and DAS28-ESR formulas (n = 56 patients)

DAS28-CRP	DAS28-ESR				
	High	**Moderate**	**Low**	**Remission**	**Total**
High	**18 (32.1%)**	0 (0%)	0 (0%)	0 (0%)	18 (32.1%)
Moderate	7 (12.5%)	**16 (28.6%)**	1 (1.8%)	1 (1.8%)	25 (44.6%)
Low	0 (0%)	4 (7.1%)	**1 (1.8%)**	2 (3.6%)	7 (12.5%)
Remission	0 (0%)	1 (1.8%)	4 (7.1%)	**1 (1.8%)**	6 (10.7%)
Total	25 (44.6%)	21 (37.5%)	6 (10.7%)	4 (7.1%)	56 (100%)

DAS28-CRP - DAS28 using CRP; DAS28-ESR - DAS28 using ESR. The values correspond to the number of people in that category (%). A patient reaches remission if DAS28 <2.6, low disease activity if $2.6 \leq DAS28 < 3.2$, moderate disease activity if $3.2 \leq DAS28 \leq 5.1$, and high disease activity if DAS28 > 5.1. Bold values indicate exact agreement between the two DAS28 formulas. Peripheral values represent individuals who were classified differently according to either formula.

The incorporation of CRP within DAS28 is due to the fact that it is a more specific and sensitive marker of inflammation. Moreover, it is less influenced by factors such as gender, age and plasma proteins (Eissa, El Shafey, Hammad, 2017). However, using the same cutoff values of the DAS28-ESR to stratify patients through DAS28-CRP into categories of disease activity has been the subject of several discussions and studies (Castrejón et al., 2008; Hensor et al., 2010; Inoue et al., 2007; Matsui et al., 2007; Sengul et al., 2015; Siemons et al., 2014; Son et al., 2016). Several researchers (Castrejón et al., 2008; Hensor et al., 2010; Inoue et al., 2007; Matsui et al., 2007; Sengul et al., 2015; Sheehy et al., 2014; Siemons et al., 2014; Son et al., 2016) have pointed to a considerable degree of disagreement between DAS28 scores regarding activity levels. The objective of the present study was to investigate the degree of agreement between the DAS28-CRP and DAS28-ESR scores in residents of southern Brazil with RA, as well as its impact on the categorization of patients regarding RA activity. The DAS28-ESR presents higher values than DAS28-CRP, producing different classifications of disease activity for the same patient, thereby preventing the interchangeability of these two instruments, as has been pointed out by several authors (Fleischmann et al., 2017; Hamann et al., 2018; Sengul et al., 2015; Sheehy et al., 2014; Siemons et al., 2014; Son et al., 2016).

In the present study, the DAS28-ESR value was higher than the DAS28-CRP value for 83.9% of the patients. Therefore, it is evident that using the DAS28-CRP may underestimate the disease activity due to its lower scores, which has also been verified by other researchers (Castrejón et al., 2008; Inoue et al., 2007; Matsui et al., 2007; Park et al., 2012; Sengul et al., 2015; Sheehy et al., 2014; Siemons et al., 2014; Son et al., 2016). If the DAS28-CRP truly underestimates disease activity, this may prevent its use in treatment strategies aimed at achieving remission. On the other hand, if the DAS28-

ESR overestimates the disease activity, patients may receive unnecessary medication when relying solely on this score. Thus, the use of any of these measures can lead to different judgments about the level of disease activity, and may lead to different therapeutic decisions. (Siemons *et al.*, 2014).

In the present study, the DAS28-CRP and DAS28-ESR showed a very strong correlation (0.922, P <0.0001), which has also been observed by other researchers (Eissa, El Shafey, Hammad, 2017). However, as observed in the discrepancy between the correlation coefficient and the dispersion diagram, a strong correlation may not signify agreement between the two methods.

The moderate strength of correlation between the unique components of the DAS28-CRP and DAS28-ESR formulas obtained here raises another important question - the weighting between the components of the formulas. Considering that the contribution of counting tender joints, swollen joints, and the subjective global health assessment are equal within the DAS28-ESR and DAS28-CRP (i.e. they have the same weighting in the algorithm), score deviations are completely attributable to differences between ESR and CRP values (Siemons *et al.*, 2014). Sengul *et al.* (2015) state that studying the relationship between the unique components of the indexes may be more appropriate than the relationship between the DAS28-ESR and DAS28-CRP because the patient's subjective overall assessment in the DAS28 may result in higher scores for disease activity. As already mentioned, there are a variety of pathophysiological conditions that influence ESR and CRP levels which should be considered when evaluating these parameters. These include age, gender, rheumatoid factor levels, the presence of comorbidities concomitant with RA, and disease duration (Matsui *et al.*, 2007; Sengul *et al.*, 2015).

The degree of moderate agreement that was observed (κ = 0.465) between the DAS28-ESR and DAS28-CRP scores has been reported in previous studies. Son *et al.* (2016) compared the two scores for 540 patients with respect to the four categories of disease activity. They obtained concordance in 344 patients (63.7%, κ = 0.45); disease activity was overestimated in 60 patients (11.1%), and in 136 patients (25.1%) disease activity was underestimated by the DAS28-CRP (Son *et al.*, 2016).

Other researchers have performed similar studies and have obtained equivalent results (Sengul *et al.*, 2015). A study by Siemons *et al.* (2014) concluded that the specific agreement by category was especially poor within the group of low disease activity, which demonstrates that this is the main range of interest when questioning the interchangeability of both scores (Siemons *et al.*, 2014). Therefore, it can be inferred that the DAS28-CRP and DAS28-ESR cannot be used interchangeably, given the differences that exist regarding the categorizations between the scores.

Eissa, El Shafey and Hammad (2017) found that, despite good correlation between the DAS28-CRP and DAS28-ESR, when stratifying patients according to activity levels there was a lower degree of agreement between the DAS28-CRP and DAS28-ESR, indicating that the current cutoff values may require modifications. In this same study, these researchers made use of the thresholds proposed by Fleischmann *et al.* in 2015 for remission and low disease activity, achieving an improvement in agreement between the DAS28-ESR and DAS28-CRP (Eissa, El Shafey, Hammad, 2017). Other studies have also suggested different DAS28-CRP values to match the threshold remission values originally proposed for the DAS28-ESR (Inoue *et al.*, 2007; Park *et al.*, 2012; Sheehy *et al.*, 2014).

Medeiros *et al.* (2015) studied the correlation between categories using the cutoff values originally proposed for the DAS28-ESR, as well as values proposed by other authors; they noted great variation between the classifications, indicating the need for further studies to establish the best measure of disease activity and better cutoff points.

Although remission, represented by DAS28 <2.6, is the primary target of treatment, there is evidence of continuous radiographic progression in patients achieving this goal (Hensor *et al.*, 2019; Jeka *et al.*, 2018; Sewerin *et al.*, 2017). With this in mind, some authors have proposed modifications in the scores in order to improve their accuracy (Baker *et al.*, 2014; Hensor *et al.*, 2019), or even the incorporation of imaging tests, such as echography and nuclear magnetic resonance, to correctly evaluate disease activity (Sewerin *et al.*, 2017). This is due to the fact that some imaging methods have

proven to be more sensitive in detecting inflammatory signals than more physical examination. In line with the current knowledge of RA as a disease that essentially causes synovial membrane inflammation, its assessment through more sensitive methods, such as imaging, may be more appropriate to reflect the effectiveness of therapy (Jeka *et al.*, 2018).

Gaujoux-Viala *et al.* (2012), (apud Eissa, El Shafey, Hammad, 2017) suggested the development of specific formulas regarding ethnic or social origin, since the development of a universal formula is improbable. Sengul *et al.* (2015) argued that although there is a need for threshold values for the DAS28-CRP it is extremely difficult to determine acceptable thresholds due to the individual characteristics of different societies (Sengul *et al.*, 2015). Thus, not only are new cutoff points necessary, these cutoff points should be validated for each population to ensure benefit when using these scores (Eissa, El Shafey, Hammad, 2017). In addition, inconsistent performances by these instruments were also found to be related to age, gender, and duration of the disease (Castrejón *et al.*, 2008; Medeiros *et al.*, 2015; Siemons *et al.*, 2014). To reduce discrepancies, a proposed solution was the incorporation of age and gender as variables in the formula (Hensor *et al.*, 2010).

The present study has some limitations. As in other studies, there was a female bias (87.5%) in the sample, which may have influenced agreement between the scores (Eissa, El Shafey, Hammad, 2017; Sengul *et al.*, 2015). The self-selection bias of the sample should also be mentioned since only less debilitated patients attended the examination – those who were most disabled did not attend due to intense pain and immobility on the scheduled date. A confounding factor to be considered is the concomitant presence of RA and fibromyalgia in some patients, who reported having more joint pain and a worse overall subjective health assessment (measured by the visual analogue scale). Since the number of tender joints and the visual analogue scale are variables that compose the DAS28 calculation it could be increased due to the concomitance with fibromyalgia.

In this study, patients with factors that could interfere with their ESR and CRP levels, such as evidence of recent infectious disease, history of malignancy, concomitant Sjögren's syndrome or other comorbidities, were not excluded. These patients have a tendency to have high values in relation to the rheumatoid factor, which can contribute to higher ESR levels (Sengul *et al.*, 2015) and interfere with results. Although such comorbidities were not used as exclusion criteria, there were no patients with such diagnoses, or who presented signs and symptoms of such pathologies, in our sample. In this study, it should be emphasized that smoking and comorbidities, such as diabetes mellitus, hypertension, coronary disease and obesity, may also influence CRP levels and should be considered when using the DAS28-CRP (Eissa, El Shafey, Hammad, 2017; Sengul *et al.*, 2015). Another limitation was the fact that this was a unicentric study, covering a population group with possibly a single ethnic trait, making it impossible to generalize our results to cover the entire Brazilian population. Further studies with a greater number of patients from different locations would result in a higher statistical power and the possibility of extrapolating the results to a wider population. We hope that this will encourage more researchers to perform studies with this purpose.

Despite its limitations, this study provides strong evidence of discrepancies between the DAS28-CRP and DAS28-ESR in patients with RA. In conclusion, although they were highly correlated, the DAS28-ESR and DAS28-CRP, differed significantly in terms of patient categorization and should not be used interchangeably. The DAS28-CRP tends to produce lower values than the DAS28-ESR, resulting in substantial differences in the classification of disease activity. The disagreement between the two scores should be emphasized, since it may directly affect the therapeutic decision in some RA cases. Therefore, when using these scores, the various clinical aspects presented by the patient should be considered, resulting in a correct interpretation of the results and an appropriate therapeutic approach.

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