Reumatismo, 2022; 74 (2): 66-72

Implication and utility of DAS-28 squeeze in rheumatoid arthritis: an Indian experience

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SUMMARY

The purpose of this study was to compare and correlate disease activity score including 28 joints counts (DAS-28) Squeeze with DAS-28 and clinical disease activity index (CDAI) to assess disease activity (DA) in rheumatoid arthritis (RA) patients.

A total of 100 RA patients were included in the study. All subjects were evaluated for disease activity using the DAS-28 Squeeze, DAS-28, and CDAI. Spearman's rho (ρ) was calculated to determine the correlation between DAS-28 Squeeze, DAS-28, and CDAI. Cross-tabulation was performed to compare and calculate the kappa coefficient for the link between two indices. For each scale, Cronbach's alpha was also calculated to test dependability.

The average age of the study group was 43.9±11.3. The mean scores on the DAS-28 Squeeze, DAS-28, and CDAI were, respectively, 3.58±1.06, 5.06±1.56, and 22.81±14.92. p=0.001 indicated a significant correlation between DAS-28 Squeeze and DAS-28 (ρ=0.986) and CDAI (ρ=0.939) for DAS-28 Squeeze. There was a considerable correlation between all three measures at various DA levels. Cronbach's alpha for DAS-28 Squeeze, DAS-28, and CDAI were respectively 0.716, 0.663, and 0.734.

DAS-28 Squeeze exhibited a substantial positive association with DAS-28 and CDAI for assessing disease activity and appears to be a more useful and reliable method than DAS-28 and CDAI for monitoring disease activity in RA patients.

Key words: *Rheumatoid arthritis, DAS-28 Squeeze, DAS-28, CDAI.*

Reumatismo, 2022; 74 (2): 66-72

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory illness of unclear etiology defined by persistent synovitis of diarthrodial joints, which results in pain, stiffness, and loss of function (1, 2). Due to the correlation between duration of active disease and severity of joint damage and disability, continuous assessment of disease activity in the clinic is important for guiding treatment (3-5). Disease activity score including 28 joints counts (DAS-28) and clinical disease activity index (CDAI) are the most often utilized disease activity evaluation methods for rheumatoid arthritis (RA) (6, 7). These indices are based on a count of 28 joints, which includes 13 joints in each of the upper limbs and one joint in each of the lower limbs, namely the knee joint, but exclude the forefeet. Consequently, these indices based on 28 joints may underestimate the real disease activity and predicted joint deterioration in RA patients with major involvement of the forefeet (8). Considering this, there should be a measure of activity that includes the forefeet in addition to the 28 joint counts. In this regard, the DAS-28 Squeeze has been designed by adding forefoot squeezing to the DAS-28 (9). Though a small number of research on DAS-28 Squeeze have been conducted internationally, no Indian study evaluating the benefits of adding the Squeeze test to DAS-28 has been conducted yet. With this information as context and the existing research gap in mind, we conducted an observational study to assess disease activity in RA patients using DAS-28 Squeeze and to correlate it with DAS-28 and CDAI.

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MATERIALS AND METHODS

From July 2014 to April 2015, a cross-sectional observational study was done in the Rheumatology Clinic of a tertiary care hospital in Haryana. The study group was prospectively enrolled with 100 RA patients diagnosed according to the American College of Rheumatology's updated 1987 criteria (10) and providing written informed consent for participation. Excluded from the study were RA patients with significant anemia, hypothyroidism, or evidence of severe renal, cardiac, liver, or pulmonary illness. All patients were evaluated for primary core data set measures, such as tender joint counts (TJC), swollen joint counts (SJC), global health by patient and by evaluator (PGA and EGA), and visual analogue scale for pain (pain VAS). Each subject's erythrocyte sedimentation rate (ESR) was determined using the Wintrobe method. From these measurements, the DAS-28 and CDAI were determined for each participant.

DAS-28 was calculated using the formula below (11):

$$DAS\text{-}28 = 0.56\sqrt{TJC} + 0.28\sqrt{SJC} + 0.70\,(\log ESR) + 0.014\,(GH)$$

CDAI was calculated with the following formula (12):

$$CDAI = TJC + SJC + PGA + EGA$$

Disease activity states for DAS-28 and CDAI are as follows: remission like state = 0.0<DAS-28≤2.6, and 0.0<CDAI≤2.8; mild = 2.6<DAS-28≤3.2, and 2.8<CDAI≤10.0; moderate = 3.2<DAS-28≤5.1, and 10<CDAI≤22.0; and severe = 5.1<DAS-28≤9.4, and 22.0<CDAI≤76.0 (7, 11-13).

All patients underwent the Squeeze test for metatarsophalangeal (MTP) joints of the feet. To execute the test, we positioned the thumb just below the first MTP joint to avoid direct joint compression and the index finger over the fifth MTP joint (Figure 1). The MTP joints were then bilaterally squeezed with a force equivalent to a handshake. If the patient sensed pain (*i.e.*, tenderness), the Squeeze test was viewed as positive; otherwise, it was read as negative.

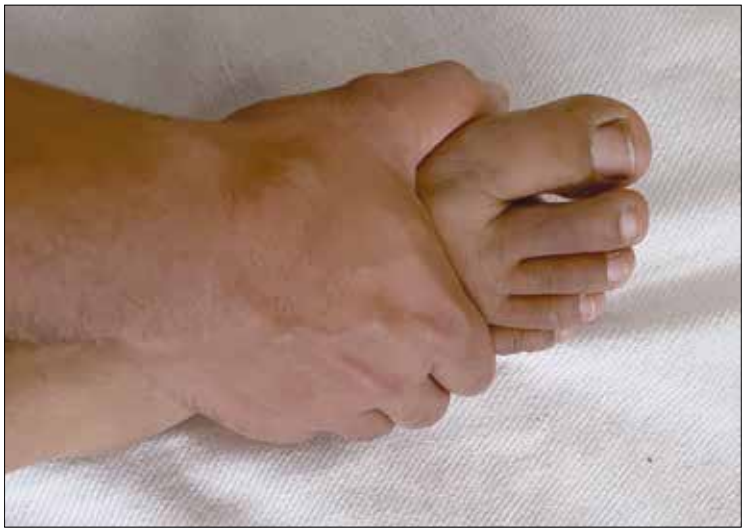

Figure 1 - The Squeeze forefoot test.

The Squeeze test was scored as follows: 0 for negative findings on both forefeet, 1 for positive results on one side, and 2 for positive results on both sides. Following this, DAS-28 Squeeze was estimated using the formula (9):

$$DAS\text{-}28\ Squeeze = 0.64 \times DAS\text{-}28 + 0.23 \times Squeeze\ test.$$

De Jong et al. define three disease activity stages for DAS-28 Squeeze as follows: below 1.6 for remission like state, ≥1.6 to below 2.4 for mild disease activity and ≥2.4 for moderate to high disease activity (9).

Statistical analysis

The acquired data were statistically analyzed using version 20 of Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA). In addition to number and percentage, descriptive data were evaluated using mean and standard deviation. DAS-28 Squeeze, DAS-28, and CDAI scores were correlated utilizing Spearman's correlation coefficient (ρ). The significance threshold was established at a p value of less than 0.05.

For the inter-scale association assessment, the study population was divided into three categories based on disease activity (remission, mild, moderate to high) and then compared using cross-tabulation and cross-com-

Table I - Mean values and standard deviation for several disease activity scales and core data set parameters for rheumatoid arthritis.

Variables (range)	Mean±SD
TJC (0-28)	9.42 ±7.74
SJC (0-28)	3.91±4.23
PGA (0-10 cm)	5.02±2.43
EGA (0-10 cm)	4.52±2.24
Pain score (0-10)	5.02±2.45
ESR (0-200 mm/hour)	32.72±16.94
DAS-28 (0-9.4)	5.06±1.56
CDAI (0-76)	22.81±14.92
DAS-28 Squeeze	3.58±1.06

RA, rheumatoid arthritis; TJC, tender joint counts; SJC, swollen joint counts; PGA, patient's global health assessment; EGA, evaluator's global health assessment; ESR, erythrocyte sedimentation rate by Wintrobe method; DAS-28, disease activity score 28; CDAI, clinical disease activity index; DAS-28 Squeeze, DAS-28 with bilateral Squeeze test.

parison. Then, kappa statistics were used to analyze the degree of agreement between DAS-28 Squeeze and other indices (DAS-28 and CDAI). The interpretation of Kappa coefficient values was as follows: <0.20 = minimal; 0.21-0.40 = fair; 0.41-0.60 = average or moderate; 0.61-0.80 = substantial and >0.81 = almost perfect. The reliability of DAS-28 Squeeze, DAS-28, and CDAI scores was determined by calculating Cronbach's alpha.

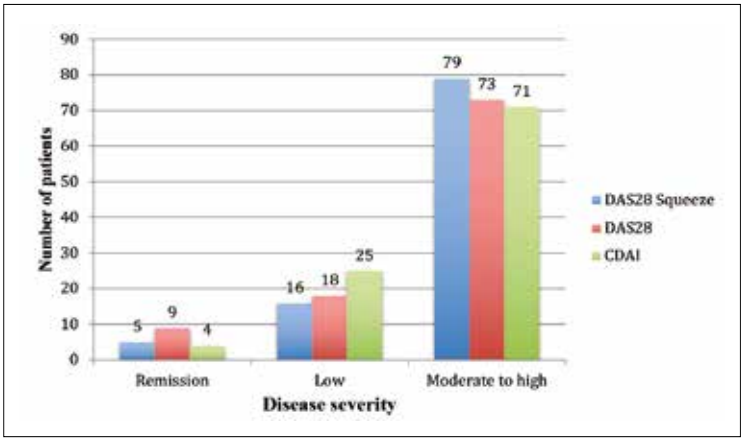

Figure 2 - Distribution of patients based on the severity of the disease as determined by various activity ratings. DAS-28, disease activity score 28; CDAI, clinical disease activity index; DAS-28 Squeeze, DAS-28 with bilateral Squeeze test.

Ethical approval

The approval of the Institution's Ethics Committee was acquired. Prior to inclusion in this trial, all patients provided written informed consent.

RESULTS

The participants' average age was 43.9±11.9 years. The sample consisted of 78% (78) females and 22% (22) males, with a female to male ratio of 3.6 to 1. The average disease duration of the study group was 69.4±55.8 months. 73 (73%) of the patients were positive for rheumatoid factor (RF), while 27 (27%) were negative. 83 (83%) patients were positive on the squeeze test. 17 (20.5%) of these 83 patients had a positive test on only one side, whereas 66 (79.5%) had positive tests on both sides. Table I displays the mean values and standard deviation for several core data set variables and disease activity indices (DAS-28, CDAI, and DAS-28 Squeeze).

Categorization of the study population according to disease activity level (remission, mild, moderate to high) using all three scales resulted in a majority of patients in the moderate to severe disease activity group (the greatest number of subjects in Group 3, *i.e*. moderate to high disease activity group) (Figure 2).

Significant relationships were found between DAS-28 Squeeze and both DAS-28 and CDAI, with coefficient values of 0.986 and 0.939, respectively (Table II). DAS-28 Squeeze was highly linked with core data set measures (TJC, SJC, PGA, EGA, Pain VAS, ESR) with coefficients (ρ) of 0.873, 0.742, 0.877, 0.885, 0.867 and 0.801, respectively (all $p<0.05$), which were nearly identical to those of DAS-28 and CDAI (Table III).

Table II - Correlation of the DAS-28 Squeeze with several disease activity parameters.

Indices/measures	(ρ)	p-value
DAS-28	0.986	<0.001
CDAI	0.939	<0.001

(ρ), Spearman's correlation coefficient; DAS-28, disease activity score 28; CDAI, clinical disease activity index; DAS-28 Squeeze, DAS-28 with bilateral Squeeze test.

Cross-tabulation and kappa statistics were implemented for agreement analysis. The Kappa values of 0.744 and 0.673 for DAS-28 Squeeze *versus* DAS-28 and DAS-28 Squeeze *versus* CDAI, respectively, suggest good agreement (Tables IV and V).
Cronbach's alpha was also calculated to determine the internal consistency of DAS-28 Squeeze and additional indices. Cronbach's alpha was 0.716 for DAS-28 Squeeze, 0.693 for DAS-28, and 0.734 for CDAI.

DISCUSSION

Regular assessment of disease activity is a crucial part of the management of RA since therapeutic decisions are dependent on disease activity at the time of routine care presentation. The measuring of disease activity in rheumatoid arthritis has a lengthy history. Various instruments or methods have been described and utilized for this purpose, such as various forms of joint counts, composite indices, acute phase reactants, global evaluation scales, pain, exhaustion, and even more general parameters such as anemia, hemoglobin, or body weight. Due to the considerable diversity of RA's presentation, course, and manifestation of distinct disease features, no one measure has been validated as the gold standard for capturing the disease activity of all RA

Table III - Correlation (ρ) between DAS-28 Squeeze, CDAI, and DAS-28 with several disease activity parameters.

Disease activity parameters	Indices			p-value
	DAS-28 Squeeze	CDAI	DAS-28	
TJC	0.873	0.943	0.881	<0.001
SJC	0.742	0.811	0.739	<0.001
PGA	0.877	0.863	0.903	<0.001
EGA	0.885	0.882	0.904	<0.001
Pain VAS	0.867	0.850	0.892	<0.001
ESR	0.801	0.718	0.826	<0.001

(ρ), Spearman's correlation coefficient; DAS-28 Squeeze, DAS-28 with bilateral Squeeze test; CDAI, clinical disease activity index; DAS-28, disease activity score 28; TJC, tender joint counts; SJC, swollen joint counts; PGA, patient's global health assessment; EGA, evaluator's global health assessment; ESR, erythrocyte sedimentation rate by Wintrobe method.

Table IV - Cross comparison between DAS-28 Squeeze and DAS-28 at varying levels of disease activity.

Level of severity		DAS-28		
		Remission (n=9)	Low (n=18)	Moderate to high (n=73)
DAS-28 Squeeze	Remission (n=5)	5	0	0
	Mild (n=16)	4	12	0
	Moderate to high (n=79)	0	6	73

Kappa=0.744; p-value <0.001. DAS-28, disease activity score 28; DAS-28 Squeeze, DAS-28 with bilateral Squeeze test; n, number of subjects.

Table V - Cross comparison between DAS-28 Squeeze and CDAI at varying levels of disease activity.

Level of severity		CDAI		
		Remission (n=4)	Low (n=25)	Moderate to high (n=71)
DAS-28 Squeeze	Remission (n=5)	3	2	0
	Mild (n=16)	1	14	1
	Moderate to high (n=79)	0	9	70

Kappa=0.673; p-value <0.001. CDAI, clinical disease activity index; DAS-28 Squeeze, DAS-28 with bilateral Squeeze test; n, number of subjects.

patients (14-16). Nonetheless, the majority of doctors and rheumatologists use the DAS-28 and CDAI to measure disease activity of RA. But, as expected, some limitations of their uses have emerged, such as the fact that none of them include feet for calculation, which may result in an underestimation of actual disease activity in RA patients with foot synovitis, and the lower specificity of DAS-28 at remission or low disease activity state (LDAS) (8).

The feet are commonly affected by both early and advanced RA. Arthritis of the foot causes reduced foot function, which is a significant cause of impairment throughout the course of the disease (17, 18). About 30% of RA patients suffer from foot and ankle arthritis (FAA) (19). FAA denotes a more severe level of disease activity and is an independent risk factor for non-remission in RA patients (19). Even forefoot involvement in early arthritis is a major indicator that RA will develop (20). According to Ajeganova et al., 70% of patients with early RA had foot synovitis within 3 years of symptom onset, and 60% of patients experienced radiographic foot damage after 8 years (21). According to van der Leeden et al., about 60% of patients with early RA reported pain and swelling in at least one MTP joint at the time of presentation; this decreased to between 40% and 50% after two years of DMARD treatment (17). Patients in a remission-like state according to the DAS-28 (based on the 28 joint count) may nevertheless have active illness in their foot (22). Therefore, an underestimation of disease activity may lead clinicians to provide inappropriate medication, which may result in rapid disease progression and, eventually, disability. Therefore, MTP joint synovitis should be evaluated alongside formal joint count to determine the true disease activity of RA. In regular practice, however, assessment of individual MTP joint synovitis is difficult and unmanageable (as in DAS), necessitating a less time-consuming alternative test that incorporates the foot in the computation. In this connection, de Jong et al. have developed, and validated DAS-28 Squeeze, which incorporates MTP joints into the activity computation (9).

There is limited DAS-28-Squeeze experience available worldwide. However, none of the research have examined its association with the DAS-28 and CDAI. Our Rheumatology clinic therefore organized and conducted this observational study.

The demographic profile of our study group was comparable to that of earlier research. In a study by Pincus et al., the average age of the patients was 53.4 years, and 81% were female (23). In a separate study conducted by de Jong et al., the mean age of the validation study group (consisting of 69% female patients) was 52 years, and 58% were RA factor positive (9). 73% RA factor positivity in our study sample was consistent with the findings of Bossert et al. (24) who identified 78% RA factor positivity in their study population. De Jong et al. (9) found Squeeze test positive in 63% of patients (21% single sided and 43% both side), whereas in the present study it was positive in 83% of patients, which may be due to high disease activity state in majority of the patients (Table IV) and longer duration of disease illness (mean value - 69.4 months) in our study group, whereas it was only 159 days i.e. 5.3 months in the study conducted by De Jong et al. (9).

In the present investigation, the mean DAS-28 Squeeze, DAS-28, and CDAI values indicated moderate to high disease activity (Table I). Similarly, the majority of patients in the study population demonstrated moderate to high disease activity (*i.e.*, group III), followed by LDAS (*i.e.*, group II) (Figure 2). Our findings revealed that the DAS-28 Squeeze measurement of disease activity was comparable to that of the DAS-28 and CDAI.

In our investigation, 4 out of 9 (or 44%) patients with a remission-like state and 6 out of 18 (33.3%) patients with LDAS were found to have low disease activity and moderate to high disease activity (*i.e.,* the next higher activity level) when measured by the DAS-28 Squeeze (Table IV). Similarly, one in four (25%) patients with a remission-like condition and nine out of twenty-five (36%) patients with LDAS ac-

cording to the CDAI were found to have LDAS and moderate to high disease activity, respectively, when evaluated using the DAS-28 Squeeze (Table V). Similarly, Wechalekar et al. observed that 43% of patients with a DAS-28-ESR of <2.6 (*i.e.*, remission-like status) had foot synovitis, and that 25-36% of patients with remission according to CDAI also had foot synovitis (25). Thus, in the current investigation, DAS-28 Squeeze demonstrated a better disease activity assessment profile than DAS-28 and CDAI, particularly in individuals with foot synovitis.

We observed a strong association when DAS-28 Squeeze was associated with DAS-28 and CDAI (Table II) as well as with core data set parameters (p value 0.001) (Table III).

Statistically significant agreements between DAS-28 Squeeze and DAS-28, as well as between DAS-28 Squeeze and CDAI, based on an investigation of agreement between two measures (Tables IV and V) were seen. Previously, de Jong et al. showed a substantial correlation (65%) between DAS-28 Squeeze and disease activity score (DAS) (9). However, in that study, it was not compared to DAS-28 (9). The DAS-28 Squeeze has the highest Cronbach's alpha of all the scales we tested. Thus, we can conclude that DAS-28 Squeeze is a reliable measure that assesses disease activity similarly to DAS-28 and CDAI, or perhaps better.

However, our study had certain drawbacks. First, the study was conducted in a single center with a relatively limited sample size. Second, fibromyalgia, which coexists in 15%-20% of RA patients, may have affected the Squeeze test outcome and, consequently, the DAS-28 Squeeze score (26). Third, we compared DAS-28 Squeeze with DAS-28 and CDAI, which do not include feet in computation, whereas before it was compared with DAS, which includes feet in calculation for disease activity assessment (12). It is unknown whether the DAS-28 and CDAI underestimate disease activity or the DAS-28 Squeeze overestimates it, resulting in different patient outcomes. However, it is also recommended that longitudinal multicenter studies with bigger sample sizes be conducted to confirm the results of our study.

CONCLUSIONS

DAS-28 Squeeze appears to be a viable instrument for quantifying disease activity and determining therapy, particularly in RA with foot involvement, as DAS-28 and CDAI may underestimate the actual disease state. In our investigation, a high positive association was found between DAS-28 Squeeze and DAS-28, CDAI, and other activity measures, demonstrating its potential for disease evaluation. Our findings are only preliminary; thus, we propose further extensive follow-up research to validate them.

Acknowledgements
None.

Conflict of interest
The authors declare no potential conflict of interest.

Funding disclosure
No funding received.

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