



## Importance of Disease Activity Indices in Indian Rheumatoid Arthritis (RA) Patients of Western Region

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Received date: June 08, 2016; Accepted date: August 01, 2016; Published date: August 05, 2016

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### Abstract

**Objectives:** Our objective was to evaluate the level of similarity between SDAI, CDAI, DAS28-ESR and DAS28-CRP in our study population which will help in the quick assessment of the disease for immediate treatment modalities.

**Methods:** The study population consisted of 38 Rheumatoid Arthritis (RA) patients attending the OPD of our hospital. After a detailed medical history and anthropometric evaluation, all the participants were subjected to biochemical analysis like CRP, ESR and their disease activity scores were calculated using DAS calculator. SDAI and CDAI were also calculated. The correlations between the four indices were studied through the Pearson's correlation coefficient (r) and the similarity between these indices was evaluated through Kendall's (K) "tau" similarity coefficient.

**Results:** The 38 RA patients were of mean age of  $42.08 \pm 12.92$  years with the disease duration of mean of 36 months (1 month- 20 years). The DAS28-ESR mean score was  $5.56 \pm 0.90$ . The DAS28-CRP mean score was  $4.93 \pm 0.86$ . The CDAI mean score was  $26.45 \pm 8.42$  and that of SDAI was  $28.20 \pm 9.08$ . A positive, statistically significant correlation was noted between the four indices for RA activity. The level of similarity between these indices was good (K variation between 0.699 and 0.910). 42.1% of the patients were classified as 'high' disease activity level, when DAS28-ESR and DAS28-CRP scores were considered together. This proportion was of 42.1%, when comparing DAS28-CRP respectively to CDAI and SDAI, compared to 60.5% when DAS28-ESR and SDAI were considered whereas DAS28-ESR and CDAI classified 65.8% of the patients as 'high' disease activity. Finally, CDAI and SDAI classified the patients upto 60.5% as having a 'high' disease activity level.

**Conclusion:** DAS28-CRP, DAS28-ESR, CDAI and SDAI correlated well for assessing the disease activity status for the RA patients. CDAI and especially SDAI have a good level of similarity with DAS28.

**Keywords:** Disease activity score; SDAI; CDAI; Rheumatoid arthritis (RA)

### Introduction

Rheumatoid Arthritis (RA) is an autoimmune inflammatory disease characterised by polyarticular inflammation of the synovial tissue. The disease activity score (DAS) is a tool to monitor disease activity in RA patients that incorporates swollen joint counts (SJC) and tender joint counts (TJC), patient's global health score and erythrocyte sedimentation rate (ESR) [1].

The first DAS was based on an examination of 44 joints and this was later followed by a reduced and simplified version based on 28 joints and hence it was called DAS28. This was recommended by American College of Rheumatology (ACR) [2]. DAS28 originally used ESR as the inflammatory marker and hence it was named as DAS28-ESR. ESR can be influenced by confounding factors such as age, sex, fibrinogen levels, hypergammaglobulinemia, rheumatoid factor, and anaemia. For these reasons, DAS28 using CRP instead of ESR was recently proposed by Fransen et al. [3], Walsh et al. [4] stated that neither age nor duration of RA influenced ESR or serum CRP levels. In 2004, Fransen

et al. predicted that DAS28 calculated with C-reactive protein (CRP) could replace DAS28-ESR in spite of the fact that cut-offs for remission and low disease activity (LDA) has not been validated for DAS28-CRP [5].

Recent data from two large observation studies suggested that DAS28-CRP tended to be lower than DAS28 ESR scores and Inoue et al. [6] suggested potential new thresholds for disease activity categories for DAS28-CRP. Wells et al. [7] validated DAS28 and EULAR response criteria based on CRP and compared them with DAS28-ESR. They concluded DAS28-CRP yielded a better EULAR response more often than DAS28-ESR [8].

RA is known to be associated with an increased risk of infection [9]. Although it is difficult to distinguish the infection risk associated with the disease from the therapy-associated infection risk, these RA-associated changes may cause the change in cellular immune response.

It has been shown that DAS can be used as a guide to study the suppression of RA disease activity with disease modifying antirheumatic drugs. And a comparison of the two DAS28 scores and the validation of the DAS28 (CRP) is necessary for clinician or patient for proper interpretation of the data so as to expect the same results as

that of DAS28 (ESR). The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have recommended regular assessment using composite clinical measures, including the Disease Activity Score (DAS), the modified Disease Activity Score-28 (DAS28), the Simplified Disease Activity Index (SDAI), and the Clinical Disease Activity Index (CDAI) [10].

The SDAI is the numerical sum of five outcome parameters: tender and swollen joint count (based on a 28 joint assessment), patient and physician global assessment of disease activity (visual analogue scale (VAS) 0–10 cm) and level of C-reactive protein (mg/dl) [11]. The SDAI is a valid and sensitive assessment of disease activity and treatment response that is comparable with the DAS28 and ACR response criteria; it is a viable tool for daytoday clinical assessment of RA treatment. Overall results indicate that the SDAI has content, criterion and construct validity. Clinical Disease Activity Index (CDAI) is a composite index (without acute-phase reactant) for assessing disease activity. The greater advantage associated with CDAI is its potential to be employed in evaluation of patients and therefore, it can essentially be used everywhere and anytime for disease activity assessment in RA patients [12].

Our objective was to evaluate the level of similarity between SDAI, CDAI, DAS28-ESR and DAS28-CRP in our study population which will help in the quick assessment of the disease for immediate treatment modalities.

## Materials and Methods

A total of 38 patients with RA, diagnosed as per the 1987 ACR (American College of Rheumatology) Classification criteria for RA [13] and after radiological analysis, were included in the study. In the event of abnormal X-ray of Chest, HRCT of chest was done for identification of infections. The patients were referred from OPD of Sir H. N. Reliance Foundation Hospital and Research Centre. The inclusion criteria include :- (1) Age above 18 years; (2) no pregnant patients; (3) HIV negative patients; (4) no past history of infection in recent past i.e. within 1 year.

All patients were evaluated for their systematic involvement. Besides this, at the time of recruitment, the physical findings such as height, weight, blood pressure, RF test, ESR, CRP, duration of the disease and DAS Score was calculated. The Patient Global Assessment (PGA) of disease activity, swelling, morning stiffness, and their medication were noted. SDAI and CDAI were also calculated.

The DAS Score is calculated by counting the number of swollen joints (out of 28) and the tender joints (out of 28). Joint swelling is soft tissue swelling, i.e., presence of synovial effusion that is detectable along the joint margins and joint tenderness is the presence of pain in a joint at rest with pressure or on the movement of the joint [14]. Published thresholds define absolute DAS-28 scores as i) remission score (<2.6), ii) mild ( $\leq 3.2$ ), iii) moderate or severe (>5.1) disease activity. The extent of response is categorized as none, moderate and good [8].

## Methods

10 ml of blood was collected through peripheral venipuncture from all the patients. ESR was determined by the Westergren method and CRP was detected by Agglutination method on Fully Automated XL-300 in a diagnostic laboratory.

Calculation and evaluation of disease activity using DAS28 ESR and DAS28 CRP according to the formula on the DAS website is represented below [15].

$$\text{DAS28-ESR} = 0.56 \times \sqrt{\text{TJC28}} + 0.28 \times \sqrt{\text{SJC28}} + 0.70 \times \ln(\text{ESR}) + 0.014 \times \text{GH}$$

$$\text{DAS28-CRP} = 0.56 \times \sqrt{\text{TJC28}} + 0.28 \times \sqrt{\text{SJC28}} + 0.36 \times \ln(\text{CRP} + 1) + 0.014 \times \text{GH} + 0.96$$

(TJC: Tender Joint Count; SJC: Swollen Joint Count; CRP: C-reactive protein; ESR: Erythrocyte Sedimentation Rate; GH: General Health on a 100 mm Visual Analogue Scale Assessment) [16].

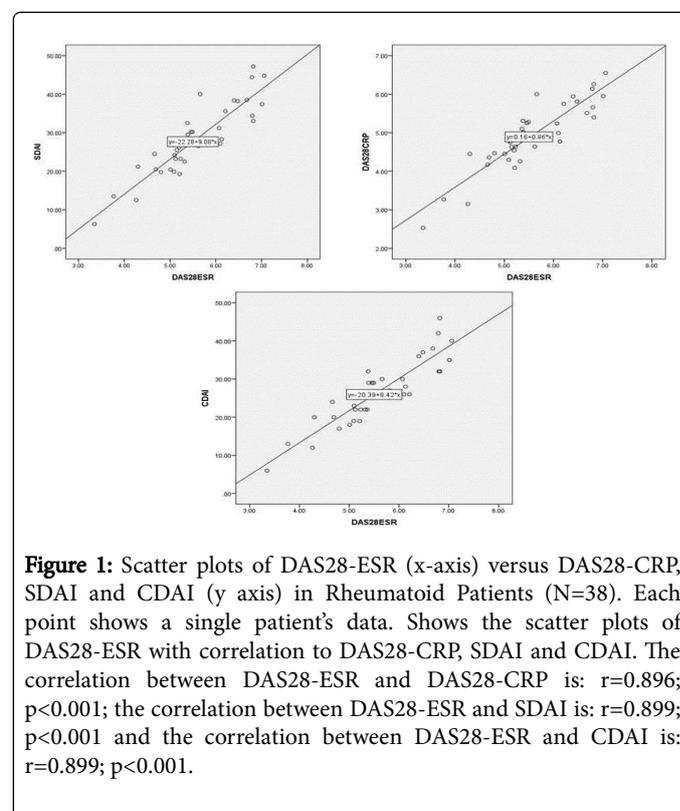
$$\text{SDAI} = \text{SJC} + \text{TJC} + \text{PGA (visual-analogue scale (VAS; in cm))} + \text{EGA (VAS (in cm))} + \text{CRP (in mg/dl)} [17].$$

$$\text{CDAI} = \text{SJC} + \text{TJC} + \text{PGA (in cm)} + \text{EGA (in cm)}$$

(PGA: Patient Global Assessment; EGA: Evaluator global assessment) [12].

## Ethics Consideration

This study was approved by the Scientific Advisory Committee and the Institutional Ethics Committee of Sir H. N. Reliance Foundation Hospital and Research Centre and informed consent was taken from the patient before the collection of their samples. The study was carried out in accordance with the “Ethical Guidelines for Biomedical Research on Human Participants, 2006” by the Indian Council of Medical Research and the Declaration of Helsinki, 2008.



## Statistical analysis

The analyses were performed using the Statistical Package for Social Sciences SPSS) software, version 21.0 (SPSS, Chicago, IL, USA). The numerical data confirmed to a normal distribution was assessed by Kolmogorov-Smirnov test and between groups comparison was done using unpaired t-test (for normal distribution). Scatter plots with linear regression line were drawn. Correlation between the four indices was assessed using Pearson's correlation coefficient(r). The similarity between the tools was evaluated through the Kendall (K) similarity coefficient "tau". The significance cut-off value (P) was fixed to 0.05 (Figure 1).

## Result

Table 1 shows the demographic data of 38 RA patients taken for our study. From Table 1, we observed that the patients were in the age group of 40-50 years with a mean age of 42.08 ± 12.92 years and the disease duration with mean of 36 months. The patients recruited were mostly females accounting to 92.11%, with M/F ratio of 3:35, disease duration of 1-240 months and the proportion of RF positivity was 59.3%. The median of the TJC count for the patients was 8.5, the median of the SJC count was 5.5, the median of ESR was 38.5 mm/hr and the median of CRP was 1.2 mg/L.

Age, years (mean ± SD)	42.08 ± 12.92
Female gender, n (%)	35/3 (92.11 %)
Disease duration, months, median (min, max)	36 (1, 240)
RF (%)	59.30%
TJC number, median (min,max)	8.5 (1, 21)
SJC,number, median (min,max)	5.5 (0, 15 )
ESR mm/hr median (min,max)	38.5( 11, 105 )
CRP mg/L, median (min,max)	1.2 (0.4, 48 )
DAS28-ESR, mean ± SD	5.56 ± 0.90
DAS28-CRP, mean ± SD	4.93 ± 0.86
SDAI, mean ± SD	28.20 ± 9.08
CDAI, mean ± SD	26.45 ± 8.42
MTX (%)	42.1
Lefno (%)	15.8
Sulpha (%)	13.2
HCQs (%)	65.8
Glucocorticoids (%)	-

**Table 1:** Demographic data showing Clinical Characteristics in Rheumatoid Arthritis Patients (N=38) RF- Rheumatoid Arthritis; TJC- Tender Joint Count; SJC- Swollen Joint Count; ESR- Erythrocyte Sedimentation Rate ; CRP- C-Reactive Protein; DAS28-ESR- Disease Activity Score-ESR; DAS28-CRP- Disease Activity Score-CRP; CDAI: Clinical Disease Activity Index; SDAI: Simplified Disease Activity Index; MTX- Methotrexate; Lefno- Leflunomide; Sulpha-Sulfasalazine; HCQs- Hydroxychloroquine

The DAS-28 ESR mean score was 5.56 ± 0.90. The mean score for DAS28-CRP was 4.93 ± 0.86

The SDAI mean score was 28.20 ± 9.08 and that of CDAI was 26.45 ± 8.42.

A total of 42.1% of patients were being treated with Methotrexate, 15.8% were being treated with Leflunomide, 13.2% were being treated with Sulphasalazine while 65.8% patients were being treated with Hydroxychloroquine. None of the patients were given Glucocorticoids.

Table 2a shows the result of rheumatoid arthritis activity scores based on the cut-off values for different indices. The cutoff values for all the four indices, are as mentioned according to Appendix by Hamdi et al. [18].

Activity scores	Mean ± SD	Activity level			
		Remission	Low	Moderate	High
<b>DAS28-ESR</b>	5.56 ± 0.90	<2.6	≤ 3.2	>3.2 et ≤ 5.1	>5.1
		n=0	n=0	n=9	n=29
<b>DAS28-CRP</b>	4.93 ± 0.86	<2.6	≤ 3.2	>3.2 et ≤ 5.1	>5.1
		n=1	n=1	n=20	n=16
<b>CDAI</b>	26.45 ± 8.42	≤ 2.8	≤ 10	>10 et ≤ 22	>22
		n=0	n=1	n=11	n=26
<b>SDAI</b>	28.20 ± 9.08	≤ 3.3	≤ 11	>11 et ≤ 26	>26
		n=0	n=1	n=14	n=23

**Table 2a:** Different activity scores and their level of activity in Rheumatoid Arthritis Patients (N=38) DAS: Disease Activity Score; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; CDAI: Clinical Disease Activity Score; SDAI: Simplified Disease Activity Index.

	DAS28-ESR	DAS28-CRP	CDAI	SDAI
<b>DAS28-ESR</b>		r=0.896 a	r=0.899 a	r=0.899 a
		K=0.699 a	K=0.732 a	K=0.727 a
<b>DAS28-CRP</b>	r=0.896 a		r=0.922 a	r=0.969 a
	K=0.699 a		K=0.769 a	K=0.854 a
<b>CDAI</b>	r=0.899 a	r=0.922 a		r=0.971 a
	K= 0.732 a	K=0.769 a		K=0.910 a
<b>SDAI</b>	r=0.899 a	r=0.969 a	r=0.971 a	
	K= 0.727 a	K=0.854 a	K=0.910 a	

**Table 2 b:** Correlations and concordance level of activity scores in Rheumatoid Arthritis Patients (N=38) P value =0.000a; DAS: Disease Activity Score; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; CDAI: Clinical Disease Activity Score; SDAI: Simplified Disease Activity Index; r: Pearson's Coefficient; K: Coefficient of Concordance (Kendall "tau").

Table 2b shows the correlation and the similarity level between the four indices of RA. A positive, statistically significant correlation was noted between the four disease activity indices of RA. The similarity level between the four indices was good (K between 0.699 and 0.910). SDAI presented the best level of similarity with the other activity indices.

Table 3 shows the comparison of the RA patients on basis of the different activity level. It represents that, 42.1% of the patients were

classified as 'high' disease activity level, when DAS28-ESR and DAS28-CRP scores were considered together. This proportion was of 42.1%, when comparing DAS28-CRP respectively to CDAI and SDAI. As regards, DAS28-ESR and SDAI, these two indices classified the patients as having a 'high' disease activity for upto 60.5% whereas DAS28-ESR and CDAI classified 65.8% of the patients as 'high' disease activity. Finally, CDAI and SDAI classified the patients upto 60.5% as having a 'high' disease activity level.

Scores	Activity level	DASCRP				CDAI				SDAI			
		Rem	Low	Mod	High	Rem	Low	Mod	High	Rem	Low	Mod	High
<b>DAS28-ESR</b>	Rem	1											
	Low		1										
	Mod		7				1	7	1			1	8
	High			13	16			4	25			6	23
					(42.1%)				(65.8%)				(60.5%)
<b>DAS28-CRP</b>	Rem												
	Low						1	1				1	1
	Mod							10	10			13	7
	High								16				16
									(42.1%)				(42.1%)
<b>CDAI</b>	Rem												
	Low										1		
	Mod											11	
	High											3	23
													(60.5%)

**Table 3:** Comparison of indices in RA patients (N=38) DAS: Disease Activity Score; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; CDAI: Clinical Disease Activity Score; SDAI: Simplified Disease Activity Index; Rem: Remission; Mod: Moderate

## Discussion

Therapy for rheumatoid arthritis has seen great progress over the past 10 years, including the approval of new drugs and the implementation of new strategies [12]. New therapeutics has revolutionized the treatment of RA, and the goal of therapy has become to maintain patients, in a low disease activity status or remission [19]. A long-term remission, normalization of physical function, and sustained quality of life are now achievable for many patients. In the western countries, the use of objective disease activity measures is commonly employed in the clinical setting for the care of individual patients. However, in India clinicians have been more reluctant to agree upon the routine use of an objective disease measure (based on either patient-reported or physician-measured outcomes) [12]. Assessing the disease activity regularly is very important aspect in the management of chronic diseases like rheumatoid arthritis (RA) but this aspect is often neglected. Moreover, in this age of expensive therapies, consistent assessment of disease activity might soon become

compulsory from the payer's perspective. Thus, the ability to adopt a simple but valid score will potentially have great implications with respect to implementation of new therapeutic concepts [20].

The composite scores or indices of disease activity are of great value in evaluation of treatment in RA patients. Such scores: (a) create better consistency in disease activity evaluation across physicians; (b) allow patients to better understand the meaning of "disease activity" by providing a single number; and (c) increase power and reduce sample size requirements in clinical trials. Importantly, consistent and frequent disease activity evaluation and consequent treatment adjustment have been shown to improve outcome, even in the short term perspective of clinical trials [21]. According to current knowledge, such intensified and prompt patient care can be expected from physicians to reduce the individual and socioeconomic impact of the disease in the longer term [12]. When using a disease activity index, it is important to focus on the disease process (level of inflammation), rather than on the consequences of disease. Response

measures are, by definition, expressed on ordinal scales, as they are designed to provide results such as 'responder versus non-responder', or 'good, moderate and non-responder'. When cut-points for response levels are applied to continuous measures, these instruments can also be used to assess treatment response. For example, to be classified as a good responder, patients must show a significant amount of improvement ( $>1.2$ ) and achieve low disease activity ( $\text{DAS28} \leq 3.2$ ) [22].

At present, one of the standard methods to measure the disease activity in patients of RA is DAS28. But this score involves a very complicated calculation, which requires a calculator and involves laboratory assistance in determining the ESR which is a contributor to the score. Hence, it is not possible to determine the disease activity immediately in a physician's chamber with DAS28, especially when a patient visits for the first time or turns non-compliant to the laboratory investigations advised, which is so common in this chronic disease [20]. The SDAI (Simplified Disease Activity Index) and its modified version, CDAI score is simple to calculate and easy to use. These indices are useful in RA clinical trials and in daily clinical setting, in the evaluation of treatment response. The small number of patients included in our study may be seen as a limited sample. So, other studies with a larger patient number should also be considered. In our study, DAS28-CRP level has a highly significant, strong linear correlation with DAS28 ESR level (correlation coefficient 0.896). This result suggests that DAS 28-CRP can be used as an alternative to DAS28-ESR.

SDAI and CDAI are simple, effective measurements of disease activity in rheumatoid arthritis and are significantly correlated with DAS28 [23]. SDAI is easy to calculate and is a viable tool for day-to-day clinical assessments. In our study, SDAI and CDAI have a strong linear correlations with DAS28-ESR (correlation coefficients of 0.899 and 0.899 respectively), which is in accordance, as stated by Aletaha et al. [17]. It stated that SDAI and CDAI had concurrent validity. Park So-Yeon et al. reported that, SDAI and CDAI had strong correlations with DAS28-ESR [23]. In accordance with data from literature, DAS28 and SDAI were significantly correlated [24]. A positive, statistically significant correlation was noted between the four indices of RA activity in the study done by Hamdi et al. [18]. Also, the level of similarity between the indices in our study are in agreement with the study conducted by Hamdi et al. SDAI presented the best similarity level with other indices. As given in Table 2b, the level of similarity between the different indices was good (K variation between 0.699 and 0.910). The strength of this study resides in comparing the level of similarity between DAS28, CDAI and SDAI for measuring disease activity in Rheumatoid Arthritis patients, which has not been done earlier in an Indian study. Only few studies have compared directly two or several of these indices.

While the literature supports that goal-directed treatments using validated instruments to assess disease activity results in improved patient outcomes, there are some limitations that should be recognized. First, the SJC and TJC in the above instruments assess only 28 joints [11]. The 28-joint counts differ from the comprehensive joint counts primarily in that they omit the feet and ankle joints. Therefore, there is a possibility that a patient with inflammation only of the feet and ankle joints could classify as being in remission according to the DAS28 remission criterion [25]. Notable exceptions to the joint evaluation are the feet, ankles and hips, which are commonly affected in RA.

## Conclusion

The various disease activity indices to evaluate the RA disability, are generally used now-a-days by the physicians. DAS28 is mostly used for evaluation of RA scores. SDAI and CDAI, have a good level of similarity with DAS28. They are easy and quick tools for assessing the activity in the patients. Our findings suggest that DAS28-CRP, SDAI, and CDAI are valid assessment indices of disease activity that are comparable with DAS28-ESR and hence DAS28 ESR can be replaced by SDAI and CDAI for better therapeutic evaluation of the patient.

## Acknowledgements

The authors wish to thank the Director and the Management of Sir H N Medical Research Society for the Funds, the Scientific Advisory Committee of Sir H N Reliance Foundation Hospital and Research Centre for sanctioning the Project and the patients for participating in this project.

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