A Proposed Composite Disease Activity Score for Extra-articular Manifestations in Rheumatoid Arthritis

BHASKAR THAKUR[1], PRASANTA PADHAN[2]

ABSTRACT

Introduction: In Rheumatoid Arthritis (RA), extra-articular disease is single most important cause of morbidity and mortality. Although DAS-28 score is used for disease assessment in RA, extra-articular manifestations are not included in the same. Therefore an initial attempt was done for development of a composite Disease Assessment Score for Extra-Articular Manifestations (DAS-EAM) based on rheumatologists consensus.

Aim: The study was an initial attempt to make a composite disease assessment score for EAMs in RA.

Materials and Methods: A hospital based cross-sectional study done on 226 RA patients with various clinical parameters with waiting scores were included to develop the DAS-EAM score. This was compared with DAS-28 and Physician's Global Assessment score and other demographic parameters and serology {RF, Anti-Cyclic Citrullinated Peptide (Anti-CCP)}. A Pearson's correlation coefficient and Kappa agreement were calculated to find out the correlation as well as agreement between DAS-EAM score, Physician's Global Assessment score and DAS-28 scores.

Results: Patient's age was significantly different among the DAS-EAM score (p=0.001). Other parameters such as gender, duration of disease and serology were not significantly associated with DAS-EAM score. There was no agreement between DAS-28 and DAS EAM score.

Conclusion: Despite the major limitations such as single centered cross-sectional study design with small sample size, this is an initial attempt for development of a composite tool for extra-articular disease in RA.

INTRODUCTION

RA is a chronic multisystem autoimmune disease predominantly involving synovial joints, affecting 1-2% of general population [1]. Disease activity is measured by DAS 28 score in RA patients. DAS 28 is a composite disease score for defining severity of RA based upon total number of swollen and tender joint counts and patient's perception of pain based upon Visual Analog Scale (VAS) (0-100 mm), calculated by using the formula: $DAS28 = 0.56 \times \sqrt{(tender\ 28)} + 0.28 \times \sqrt{(swollen\ 28)} + 0.70 \times \ln(ESR) + 0.014 \times VAS$ [2]. Extra articular disease, seen in about 40% RA patients, is the single most important cause of morbidity and mortality in RA [3]. Extra articular involvement is common in various stages of the disease [4]. However till date, there is no tool to access the severity of extra articular manifestations in RA. DAS, also known as Disease Activity Score, in RA combines the information from Swollen joints, Tender joints, acute phase response and patients' global assessment as a single continuous measure for the disease activity in RA [5].

Physician's Global Assessment, also called as Physician's Global is a standardised data set which includes a 0-10 continuous VAS for recording. The values in 0-1 range indicates controlled or equivocal RA disease activity, and values in the 1.1-4, 4.1-8, and 8.1-10 ranges for mild, moderate, and high activity respectively [6].

Extra-Articular Manifestations (EAMs) are difficult to diagnose and treat since no clear consensus exists among the rheumatologists for their correct classification and also due to the fact that there are no guidelines available for their treatment. Therefore the aim of the current study was to make a composite score for EAM in RA.

MATERIALS AND METHODS

This was a tertiary care teaching hospital based cross-sectional study conducted in Bhubaneswar, Odisha, India. After obtaining informed consent from all the patients who fulfilled 2010 ACR/EULAR classification criteria for RA [7] between the age group 18 to 60 years were included in the study. The patients with co-morbidities such as chronic airway diseases, liver diseases, renal diseases, diabetes mellitus, hypertension, hypothyroidism, current or past pulmonary tuberculosis, and connective tissue diseases other than RA, pregnant women were excluded from the study.

A total of 226 consecutive eligible patients with RA who attended the Outpatient Department (OPD) of rheumatology from 1st June 2018 to 30th December 2018 were included in this study. The study was approved by the Institutional Ethics Committee of the medical college (Kalinga Institute of Medical Sciences) (approval number KIMS/KIIT/69/2016 dated 22-09-2016).

Information on demographic and clinical characteristics such as sex, age, duration of disease, diagnosis, co-morbidities were collected. A complete physical, clinical examination and biochemical investigation (ESR, CRP, RF and Anti CCP) were done in each patient. Extra-articular disease parameters namely Skin Ulcer/Gangrene, Interstitial Lung Disease (ILD), Retinal Vasculitis, Scleromalacia, Coronary Artery Disease (CAD), Mononeuritis Multiplex, CNS Vasculitis, Nephritis, Amyloidosis, Felty/LGL Syndrome, Cord Compression, Lymphoma, Petechiae/Purpura, Pleurisy/Pleural Effusion, RA Lung Nodules, Scleritis/Episceritis, Valvular Heart disease, Myositis, Raynaud's Phenomenon, RA Skin Nodules, Kerato Conjunctivitis Sicca (KCS), Pericarditis/Pericardial Effusion, Carpal Tunnel Syndrome, Anaemia, Thrombocytosis, Lymphadenopathy, Splenomegaly and Fever were assessed. Additionally, Physician's Global Assessment Score and DAS 28 Score were also assessed and obtained for every patient; which are freely available for routine clinical use [6,8].

Weighting and Scoring

Based on the consensus of three well experienced rheumatologists, parameters for extra-articular disease, their weight and score were decided. A total of 28 extra-articular disease parameters were

selected based on various common extra articular disease in RA, which were further grouped into 4 broader categories reflecting the importance of each parameter in the physicians' ratings of disease activity and a weighting of 1, 2, 4 and 8 was assigned to each of the abnormal parameter which reflected their clinical importance [Table/Fig-1]. These weights were thought to be easier to remember for clinical use and a composite score based on these weights were compared with Physician's Global Assessment score where the patients were reclassified into 3 groups; mild (VAS 1.1-4) with a score of 1, moderate (VAS 4.1-8) with a score of 2, and high disease activity (VAS 8.1-10) with a score of 3. This was considered as gold standard, as there is no such previous published literature on extra-articular RA assessment.

Descriptor	Weight	Scores
Skin ulcer/Gangrene	8	8 if present otherwise 0
ILD	8	8 if present otherwise 0
Retinal vasculitis	8	8 if present otherwise 0
Scleromalacia	8	8 if present otherwise 0
CAD	8	8 if present otherwise 0
Mononeuritis multiplex	8	8 if present otherwise 0
CNS vasculitis	8	8 if present otherwise 0
Nephritis	8	8 if present otherwise 0
Amyloidosis	8	8 if present otherwise 0
Felty/LGL syndrome	8	8 if present otherwise 0
Cord compression	8	8 if present otherwise 0
Lymphoma	8	8 if present otherwise 0
Petechiae/Purpura	4	4 if present otherwise 0
Pleurisy/Pleural effusion	4	4 if present otherwise 0
RA lung nodules	4	4 if present otherwise 0
Sceleritis/Episceritis	4	4 if present otherwise 0
Valvular heart disease	4	4 if present otherwise 0
Myositis	4	4 if present otherwise 0
Raynaud's phenomenon	2	2 if present otherwise 0
RA skin nodules	2	2 if present otherwise 0
KCS	2	2 if present otherwise 0
Pericarditis/Pericardial effusion	2	2 if present otherwise 0
Carpal tunnel syndrome	2	2 if present otherwise 0
Anaemia	1	1 if present otherwise 0
Thrombocytosis	1	1 if present otherwise 0
Lymphadenopathy	1	1 if present otherwise 0
Splenomegaly	1	1 if present otherwise 0
Fever	1	1 if present otherwise 0
Total maximum possible scores		135

[Table/Fig-1]: Disease activity index extra-articular manifestations in rheumatoid arthritis.

Hence, each individual was allocated a risk score. Patients were classified as no risk associated with score 0, low risk with a score range from 1 to 3, medium risk with a score range 4 to 8 and high risks associated with a score of more than 8 based on the consensus of rheumatologists (at least 10 years of expertise in the field).

STATISTICAL ANALYSIS

All the categorical parameters were reported as frequency and percentage whereas continuous parameters were presented in Mean±SD (Standard Deviation). Categorical parameters were compared among the various risk group using either Chi-square test or Fisher's-exact test and continuous parameters were compared by One-Way Analysis of Variance (ANOVA) and Kruskal Wallis ANOVA followed by a multiple comparison test using Bonferroni adjustment. The Spearman's Rank correlation Coefficient test was applied to find out the relationship between Physician's Global Assessment

score and DAS-EAM score. A quantification of Pearson's correlation coefficient and scatter plot were shown between original DAS-28 and calculated composite scores. A Kappa statistics was performed to quantify the agreement between classified DAS-28 and classified composite score.

Data were analysed using standard statistical software Stata 15.1. A p-value of <0.05 was considered as statistical significant.

RESULTS

Different socio-demographic and biochemical parameters for a total of 226 RA patients have been summarised in [Table/Fig-2].

Parameters	Summary
Age (in years); Mean±SD	49.4±11.8
Disease duration (in months);	
Mean±SD	89.7±77.6
RF; n (%)	
Negative	11 (10.6)
Positive	92 (89.3)
Anti CCP; n (%)	
Negative	5 (6.7)
Positive	70 (93.3)
Presence of either of RF or Anti-CCP; n (%)	
Negative	4 (3.4)
Positive	114 (96.6)
Sex; n (%)	
Male	21 (9.3)
Female	205 (90.7)

[Table/Fig-2]: Summary of socio-demographic and biochemical parameters for 226 Rheumatoid Arthritis patients.

[Table/Fig-3] shown that 50% of the patients were Anaemic followed by Kerato Conjunctivitis Sicca (12.8%), Lymphadenopathy (8.85%), Interstitial Lung Disease (8.41%), RA Skin Nodules (6.64%), Carpal Tunnel Syndrome (6.19%), fever (3.1%) and Thrombocytosis (1.78%). CAD, Mononeuritis Multiplex, Scleromalacia and Pleurisy/Pleural Effusion were found in less than 1% of patients. Other EAM parameters namely Skin Ulcer/Gangrene, Retinal Vasculitis, CNS Vasculitis, Nephritis, Amyloidosis, Felty/LGL Syndrome, Cord Compression, Lymphoma, Myositis Petechiae/Purpura, RA Lung Nodules, Sceleritis/Episceritis, Valvular Heart Disease, Raynaud's Phenomenon, Pericarditis/Pericardial Effusion, and Splenomegaly were not present.

EAM parameters	N (227)	%
Anaemia	113	50
KCS	29	12.8
Lymphadenopathy	20	8.85
ILD	19	8.41
RA skin nodules	15	6.64
Carpal tunnel syndrome	14	6.19
Fever	7	3.1
Thrombocytosis	4	1.78
CAD	2	0.9
Mononeuritis multiplex	2	0.88
Scleromalacia	1	0.44
Pleurisy/Pleural effusion	1	0.44

[Table/Fig-3]: Presentation of various extra-articular manifestations in rheumatoid arthritis patients.

[Table/Fig-4] shows the mean and standard deviation of DAS-28 (3.58±1.27) and DAS-EAM score (2.03±2.90) among rheumatoid arthritis patients. Additionally frequency distribution is reported with

different cut-offs of DAS-28 and DAS-EAM score. According to physician global assessment scale, extra-articular manifestations among RA patients is also described in [Table/Fig-4].

| Scores to predict EAM	Mean±SD; n(%)
DAS-28 score;	3.58±1.27
≤3.2 (Mild)	99 (45.0)
3.2-5.1 (Moderate)	96 (43.6)
>5.1 (Severe)	25 (11.4)
Physical global assessment score	n (%)
0-Controlled RA	50 (22.4)
1-Mild	95 (42.6)
2-Moderate	74 (33.2)
3-Severe	04 (1.79)
DAS-EAM score; Mean±SD	2.03±2.90
0	82 (36.4)
1-3	109 (48.5)
4-8	20 (8.9)
>8	14 (6.2)

[Table/Fig-4]: Level of different Clinical Scores to predict extra-articular manifestations in rheumatoid arthritis patients.

[Table/Fig-5] shows that among RA patients, increasing age had significantly higher DAS-EAM score. The duration of disease was not statistically significant. Presence of RF and/or Anti-CCP did not influence DAS EAM score. There was no influence of gender on DAS-EAM score.

| Parameters | DAS-EAM score classification | | | | p-value |
	0	1- 3	4-8	>8	
Age (in years); Mean±SD	49.4±12.3	47.1±10.9	55.5±12.2	57.2±9.0	0.001
Disease duration (in months);					
Mean±SD	82.7±74.5	84.5±74.1	101.5±64.2	135.4±97.2	0.079
RF; n (%)					
Negative (11)	3 (27.3)	8 (72.7)	0 (0.0)	0 (0.0)	0.526
Positive (91)	23 (25.0)	48 (52.2)	11 (12.0)	10 (10.9)	
Anti CPP; n (%)					
Negative (5)	3 (60.0)	2 (40.0)	0 (0.0)	0 (0.0)	0.551
Positive (68)	22 (31.4)	36 (51.4)	4 (5.7)	8 (11.8)	
Any positive of RF or Anti-CCP					
Negative (4)	2 (50.0)	2 (50.0)	0 (0.0)	0 (0.0)	0.841
Positive (112)	32 (28.1)	59 (51.7)	11 (9.7)	12 (10.5)	
Sex					
Male	9 (42.9)	9 (42.9)	2 (9.5)	1 (4.8)	0.900
Female	73 (35.8)	100 (49.0)	18 (8.8)	13 (6.4)	

[Table/Fig-5]: Association of different socio-demographic and biochemical parameters with DAS-EAM score.
Tests applied-One-way ANOVA, Kruskal-Wallis ANOVA and Fisher's-exact test

A correlation coefficient between Physician's global assessment score and DAS-EAM score was observed as 0.32 with p-value of <0.001, as depicted in [Table/Fig-6] as scatter plot diagram. Additionally an agreement between Physician global assessment score and DAS-EAM score was observed as 41% (Kappa value =0.12) with p-value of 0.002 which was a significant moderate agreement. The agreement between DAS-28 and DAS-EAM score was observed as 21.5% (Kappa= -0.06) with p-value 0.983 which indicated no agreement between these two scores. The correlation coefficient between DAS 28 and DAS-EAM score was observed as 0.283 with p-value of <0.001. Also, scatter plot in [Table/Fig-7] clearly demonstrated that DAS-28 and DAS-EAM score were not linearly related.
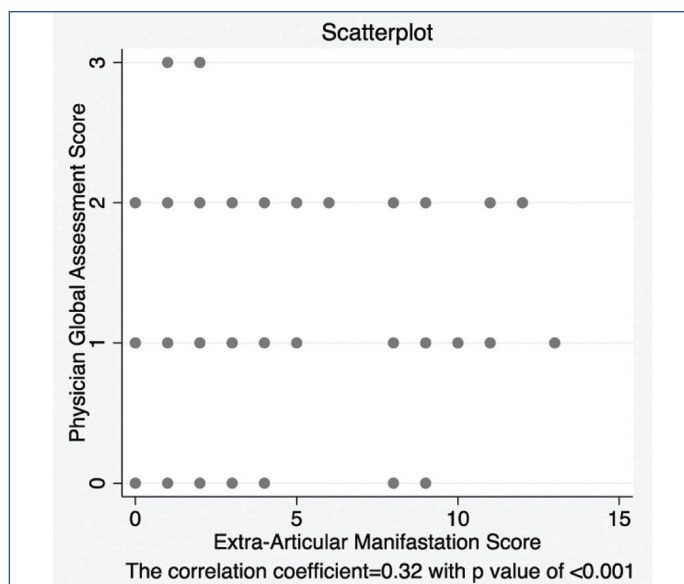
[Table/Fig-6]: Scatter plot between Physician's Global Assessment score and DAS EAM Scores.
*Spearman's Rank correlation
(The correlation coefficient r=0.32 with p-value of <0.001)
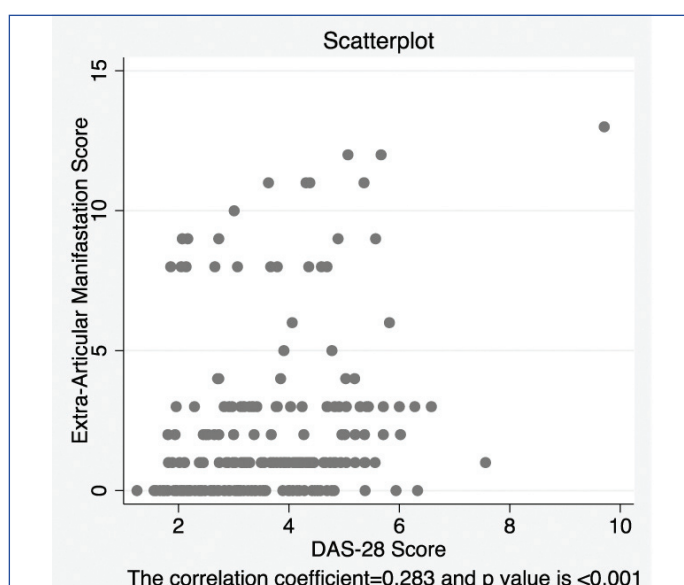
[Table/Fig-7]: Scatter plot between DAS-EAM score and DAS 28 Scores.
*Pearson's correlation coefficient
(The correlation coefficient r=0.283 and p-value is <0.001)

DISCUSSION

In the study, though the correlation coefficient was found to be significant, there was no clinically meaningful correlation pattern between DAS-28 and DAS-EAM score depicted in the scatterplot. Also, the observed non-significant agreement between these two entities clearly indicates the present scoring system for disease activity in RA based on solely joints counts is not enough to predict the presence and severity of extra-articular disease. A DAS-EAM score in each RA patient should be a mandatory tool for composite disease assessment in addition to DAS-28.

It was found that the increasing age of the patients had a significant correlation with the DAS-EAM score. This is again related to the fact that in rheumatoid arthritis, the presence of extra-articular disease and co-morbidities in elderly could influence adverse outcome in these population. This finding is similar to study by Inbanathan J et al., where older age group patients had more extra-articular manifestations [9].

Serology, RF, and Anti-CCP antibodies did not influence the DAS-EAM score. This is contrary to previous literature which indicates DAS-EAM scoring is mandatory tool for assessment of extra-articular disease and its outcome and not the mere presence or absence of

either RF or Anti-CCP [10]. Similarly gender did not influence our DAS-EAM score, though RA is more common in females.

Longer duration of disease is often associated with more extra-articular manifestations in RA and more cardiovascular events [11,12]. However in current study, this was again not found to be significant in comparison to DAS-EAM score which could be due to smaller sample size.

Physician's Global Assessment score and DAS-EAM score had a significant positive correlation in this study. Hence the importance of inclusion of Physician's Global Assessment score in DAS-EAM score could be a better tool for assessment of extra-articular disease in RA.

LIMITATION

The study has following limitations such as small sample size, single centre and cross-sectional study. In general, for assessment of disease activity in RA, a longitudinal study is warranted. However, this is the only and earliest attempt for extra-articular disease activity in RA. Hence, a multi-centric prospective study with validation model for the same is suggested.

CONCLUSION

DAS-EAM score can be a useful tool to monitor extra-articular disease severity in RA. Prospective validation for the same is warranted for future clinical use.

REFERENCES

[1] Lee DM, Weinblatt ME. Rheumatoid arthritis. Lancet. 2001;358(9285):903-11.

[2] Prevoo ML, Van'T Hof M, Kuper HH, Van Leeuwen MA, Van De Putte LB, Van Riel PL. Modified disease activity scores that include twenty-eight-joint counts development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis & Rheumatism. 1995;38(1):44-48.

[3] Young A, Koduri G. Extra-articular manifestations and complications of rheumatoid arthritis. Best practice & research Clinical Rheumatology. 2007;21(5):907-27.

[4] Das S, Padhan P. An overview of the extraarticular involvement in rheumatoid arthritis and its management. Journal of pharmacology & pharmacotherapeutics. 2017;8(3):81.

[5] Van der Heijde DM, van't Hof MA, Van Riel PL, Theunisse LA, Lubberts EW, van Leeuwen MA, et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. Annals of the Rheumatic Diseases. 1990;49(11):916-20.

[6] Felson DT, Anderson JJ, Boers M, Bombardier C, Chernoff M, Fried B, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. Arthritis & Rheumatism. 1993;36(6):729-40..

[7] Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham III CO, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis & Rheumatism. 2010;62(9):2569-81.

[8] van Gestel AM, Haagsma CJ, van Riel PL. Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology. 1998;41(10):1845-50.

[9] Inbanathan J, Suneetha DK, Harsha G, George M, Shashank MS. Extra-articular Manifestation of Rheumatoid Arthritis. International Journal of Scientific Study. 2016;4(1):81-84.

[10] De Rycke L, Peene IS, Hoffman IE, Kruithof E, Union A, Meheus L, et al. Rheumatoid factor and anticitrullinated protein antibodies in rheumatoid arthritis: diagnostic value, associations with radiological progression rate, and extra-articular manifestations. Annals of the Rheumatic Diseases. 2004;63(12):1587-93.

[11] Cojocaru M, Cojocaru IM, Silosi I, Vrabie CD, Tanasescu R. Extra-articular manifestations in rheumatoid arthritis. Maedica. 2010;5(4):286.

[12] Turesson C, McClelland RL, Christianson TJ, Matteson EL. Severe extra-articular disease manifestations are associated with an increased risk of first ever cardiovascular events in patients with rheumatoid arthritis. Annals of the Rheumatic Diseases. 2007;66(1):70-75.

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Biostatistics, Kalinga Institute of Medical Sciences, KIIT University, Bhubaneswar, Odisha, India.
2. Associate Professor, Department of Rheumatology, Kalinga Institute of Medical Sciences, KIIT University, Bhubaneswar, Odisha, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Prasanta Padhan,
Department of Rheumatology, Kalinga Institue of Medical Sciences, KIIT University, Bhubaneswar, Odisha, India.
E-mail: prasanta.padhan@gmail.com

AUTHOR DECLARATION:
• Financial or Other Competing Interests: No
• Was Ethics Committee Approval obtained for this study?   Yes
• Was informed consent obtained from the subjects involved in the study?   Yes
• For any images presented appropriate consent has been obtained from the subjects.   NA