

Disease activity measurement in rheumatoid arthritis: comparison of 3 disease activity index tools at Kenyatta National Hospital

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Abstract

Objectives: To compare the congruence of the Disease Activity Score with 28-joint count (DAS-28) with the Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI) in measuring disease activity in Rheumatoid Arthritis (RA) patients at the Kenyatta National Hospital (KNH).

Design: Cross-sectional descriptive study.
Setting: Rheumatology Out-Patient Clinic (ROPC) at KNH.

Subjects: One hundred and four patients who fulfilled the 2012 American College of Rheumatology Classification Criteria for RA.

Results: DAS28, SDAI and CDAI were significantly correlated with each other on a group level ($p < 0.001$). Internal consistency was highest for CDAI ($\alpha = 0.705$) and lowest for DAS28 ($\alpha = 0.67$). Kappa statistics revealed substantial degree of agreement with respect to controlled, active, moderate and high disease activity categories according to the three scores.

Conclusion: Both SDAI and CDAI proved to be in congruence with DAS28 in daily clinical routine. SDAI and CDAI were found to be more stringent in defining remission.

Introduction

It has been recognized for decades that survival among persons with RA is significantly worse compared to survival in the general population¹. Premature death has been long recognized as a manifestation of RA¹. The cause of these premature deaths include a higher risk of several serious co morbid conditions with worse outcomes after the occurrence of these illnesses, sub-optimal primary or secondary preventive care and the systemic inflammation and immune dysfunction associated with RA appears to promote and accelerate co morbidity and mortality¹. It is also established that duration of active disease is associated with joint damage and disability². Therefore, early initiation of treatment and continuous monitoring of disease activity is needed to reduce structural damage in RA². The current treatment approach for patients with RA

involves early initiation of aggressive therapy with Disease Modifying Anti-Rheumatic Drugs (DMARDs) and biologic agents³. The goal of treatment is remission and therefore regular assessment of disease activity is necessary in the clinic for guiding treatment⁴. In this respect, the patients should understand the term ‘disease activity’ as they understand glucose values or blood pressure in diabetes and hypertension, respectively². This can be the key to success of and compliance to therapy. Numerous RA disease activity measurement tools are currently available for use⁵. Since the 1950’s when the first composite disease activity measurement tool for use in RA was developed⁶, many attempts have been made to improve RA disease activity monitoring. The psychometric data related to these tools have been published over the course of decades and across numerous journals⁵. The last two decades have witnessed a dramatic improvement in the treatment of RA, with disease remission now considered a realistic goal for most patients⁷. Surrogate measures of outcome such as disease activity index measures can facilitate clinical decision making to achieve these goals and studies in RA show that treating to target improves outcome⁸⁻¹⁰. Though there are 63 currently available RA disease activity measurement tools, three are commonly used¹¹; CDAI, DAS28 (Erythrocyte Sedimentation Rate or C-Reactive Protein) and SDAI. All three produce a single continuous index and have defined ranges for indicating mild, moderate or high disease activity or clinical remission. By applying these tools systematically in clinical practice, physicians are able to “treat to target” and effectively implement the ACR and EULAR recommendations for the treatment of RA³. Given the heterogeneity of settings in which healthcare is delivered to patients with RA, these measures offer a full range of data collection options. This study intends to compare the performance of the three disease activity measurement tools i.e. DAS-28, SDAI and the CDAI in a clinical routine setting with the aim of recommending routine use of SDAI and CDAI during every visit to the rheumatology outpatient clinic.

Materials and Methods

This was a hospital based study done between January 29th and March 9th 2015, at the rheumatology out-patient clinic of KNH. A minimum sample of 101 patients was required. The subjects were patients aged 18 years and older fulfilling the 2012 ACR classification criteria for RA.

Targeted clinical history was taken followed by joint assessment out of a 28-joint count. The patient global assessment of general health (on a scale of 0-100mm for DAS-28 and 0-10cm for SDAI and CDAI) and the provider general assessment of general health for SDAI and CDAI only (on a scale of 0-10cm) were carried out. Approximately 4ml of venous blood was drawn aseptically, following standard guidelines from each patient for measurement of quantitative C-Reactive Protein (CRP).

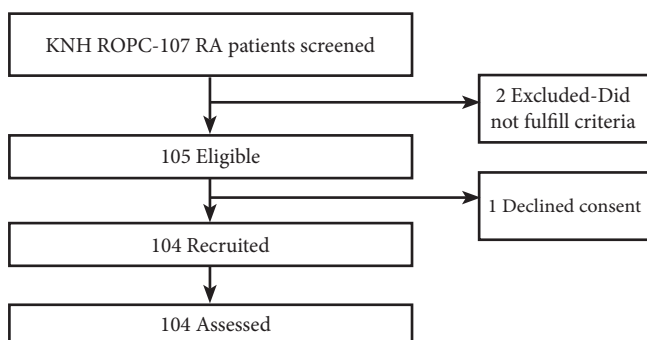
Calculation of disease activity scores was then calculated as per the specific guide for each tool. Patients were then categorized as having controlled disease (remission + low disease activity) or active disease (moderate and high disease activity) and as being in remission, having low, moderate or high disease activity using the following cut-off points: DAS-28 (≤ 2.6 for remission, ≤ 3.2 for low, ≤ 5.1 for moderate and 5.1 for high), SDAI (≤ 3.3 for remission, ≤ 11 for low, ≤ 26 for moderate and > 26 for high) and CDAI (≤ 2.8 for remission, ≤ 10 for low, ≤ 22 for moderate and > 22 for high).

Spearman's rank correlation coefficient was used to test the congruency and agreement of the tools at the group level while kappa statistics was used to test for that between the disease categories.

Results

In this ten week-time based study (January 29th to March 9th 2015) targeting RA patients attending the KNH ROPC, 106 patients confirmed to have RA (2012 ACR classification criteria and confirmed by a rheumatologist) were consecutively screened for recruitment. Two patients were not eligible for the study after declining to give consent (Figure 1).

Figure 1: Demographic characteristics of the study population



The mean age of the patients was 48.7 years (SD = 15.6). Most of the study participants were female 93 (89.4%) giving a female to male ratio of 9:1 (Table 1).

Table 1: Clinical characteristics of the study population

| Variable | Frequency (%) |
|------------------------|---------------|
| Mean age in years (SD) | 48.7 (15.6) |
| Gender | |
| Female | 93 (89.4) |
| Male | 11 (10.6) |
| Level of education | |
| None | 9 (8.7) |
| Primary | 41 (39.5) |
| Secondary | 26 (25.0) |
| Tertiary | 28 (26.9) |
| Marital status | |
| Single | 17 (16.3) |
| Married | 71 (68.3) |
| Separated | 2 (1.9) |
| Divorced | 1 (1.0) |
| Widowed | 13 (12.5) |

Ninety six point two per cent of the patients had had RA disease symptoms for more than 1 year while 82.7% had had a diagnosis of RA for the same period. Eighty six point five per cent of the patients were on DMARDS and 62.5% were on steroids. A good proportion of the patients on steroids had controlled disease (Table 2).

Table 2: Disease activity scores

| Variable | Frequency (%) |
|----------------------------------|---------------|
| Duration since diagnosis (years) | |
| <1 | 18 (17.3) |
| 1-5 | 51 (49.0) |
| >5 | 35 (33.7) |
| Duration of symptoms (years) | |
| <1 | 4 (3.8) |
| 1-5 | 45 (43.3) |
| >5 | 55 (52.9) |
| NSAIDs | |
| Yes | 60 (57.7) |
| No | 44 (42.3) |
| Steroids | |
| Yes | 65 (62.5) |
| No | 39 (37.5) |
| DMARDS | |
| Yes | 90 (86.5) |
| No | 14 (13.5) |

The median disease activity score of the study population was 3.5 (IQR: 2.5-4.7) i.e. moderate disease activity. That of SDAI and CDAI was 14.1(IQR: 7.7-25.9) and 11.0(IQR: 6.0-20.7) respectively, both signifying moderate disease activity (Table 3).

Table 3: Disease activity categories

| | Median (IQR) |
|-------|-----------------|
| DAS28 | 3.5 (2.5-4.7) |
| SDAI | 14.1 (7.7-25.9) |
| CDAI | 11.0 (6.0-20.7) |

There is significant congruence of SDAI and CDAI with DAS28 for moderate and high disease activity categories. DAS28 over-classifies patients as being in remission by redistributing them from the low disease activity category. SDAI and CDAI are in almost perfect

agreement for all disease activity categories. When disease activity is categorized as either controlled or active disease, the three tools show significant agreement to one another (Table 4).

Table 4: Correlation amongst the disease activity score tools

| Disease activity | DAS28 | | SDAI | | CDAI | |
|------------------|-----------|------------|-----------|------------|-----------|------------|
| | n (%) | 95% CI | n (%) | 95% CI | n (%) | 95% CI |
| Remission | 32 (30.8) | 21.2, 40.4 | 7 (6.7) | 2.9, 11.5 | 10 (9.6) | 3.8, 16.3 |
| Low | 12 (11.5) | 5.8, 17.3 | 32 (30.8) | 22.1, 39.4 | 38 (36.5) | 26.9, 45.2 |
| Moderate | 41 (39.4) | 30.8, 49.0 | 39 (37.5) | 27.9, 47.1 | 31 (29.8) | 21.2, 38.5 |
| High | 19 (18.3) | 10.6, 26.0 | 26 (25.0) | 17.3, 33.7 | 25 (24.0) | 16.3, 31.7 |
| Controlled | 44 (42.3) | 32.7, 51.9 | 39 (37.5) | 27.9, 46.2 | 48 (46.2) | 36.5, 55.8 |
| Active | 60 (57.7) | 48.1, 67.3 | 65 (62.5) | 53.8, 72.1 | 56 (53.8) | 44.2, 63.5 |

The correlation coefficient between DAS28 and SDAI was 0.960 while that between DAS28 and CDAI was 0.892 which were both statistically significant with a $p < 0.001$ (Table 5).

Table 5: Correlation at the group level

| | Spearman's rank coefficient (rho) | P value |
|------|-----------------------------------|---------|
| SDAI | 0.960 | <0.001 |
| CDAI | 0.892 | <0.001 |

The agreement of DAS28 and SDAI in disease activity categorization revealed a kappa value of 0.78 while that of DAS28 and CDAI was 0.69 both of which were statistically significant with $p < 0.001$ (Tables 6 and 7).

Table 6: Agreement of disease activity categorization between DAS28 and SDAI

| Disease activity | DAS28 | SDAI | Spearman's rank (rho) | P value |
|------------------|------------------|---------------------|-----------------------|---------|
| Controlled | 2.28 (1.79-2.52) | 5.80 (3.99-8.04) | 0.850 | <0.001 |
| Active | 4.51 (3.77-5.44) | 24.71 (17.00-34.86) | 0.912 | <0.001 |

Table 7: Agreement of disease activity categorization between DAS28 and CDAI

| | DAS28 | | Total | McNemar's p value | Measure of agreement Kappa, p value |
|--------------------|------------|--------|-------|-------------------|-------------------------------------|
| | Controlled | Active | | | |
| SDAI | | | | 0.227 | 0.78, <0.001 |
| Controlled disease | 36 | 3 | 39 | | |
| Active disease | 8 | 57 | 65 | | |
| Total | 44 | 60 | 104 | | |

Table 8: Multivariate analysis

| Variable | DAS28 | | OR (95% CI) | P value |
|----------------|-------------|-------------|---------------|---------|
| | Controlled | Active | | |
| Age, mean (SD) | 48.0 (15.7) | 49.2 (15.7) | - | 0.695 |
| Sex | | | | |
| Female | 41 (44.6%) | 51 (55.4%) | 2.1 (0.5-8.6) | 0.345 |
| Male | 3 (27.3%) | 8 (72.7%) | | |
| NSAIDs | | | | |
| Yes | 25 (41.7%) | 35 (58.3%) | 0.9 (0.4-2.1) | 0.877 |
| No | 19 (43.2%) | 25 (56.8%) | | |
| Steroids | | | | |
| Yes | 25 (38.5%) | 40 (61.5%) | 0.7 (0.3-1.5) | 0.305 |
| No | 19 (48.7%) | 20 (51.3%) | | |
| DMARDs | | | | |
| Yes | 38 (42.2%) | 52 (57.8%) | 1.0 (0.3-3.0) | 0.964 |
| No | 6 (42.9%) | 8 (57.1%) | | |
| DOS | | | | |
| <1 | 1 (25.0%) | 3 (75.0%) | 1.0 | 0.641 |
| 1-5 | 21 (46.7%) | 24 (53.3%) | | |
| ≥5 | 22 (40.0%) | 33 (60.0%) | | |
| DOD | | | | |
| <1 | 5 (27.8%) | 13 (72.2%) | 1.0 | 0.362 |
| 1-5 | 24 (47.1%) | 27 (52.9%) | | |
| ≥5 | 15 (42.9%) | 20 (57.1%) | | |

There was no significant association between disease activity as scored using the three tools with gender, treatment modality, duration of symptoms (DOS) or duration of disease (DOD) as shown in Table 8.

Discussion

The main aim of this study was to evaluate the correlation and agreement between the DAS-28 with SDAI and the CDAI tools in routine assessment of disease activity in RA patients attending KNH ROPC in daily clinical routine.

The study also set out to establish the utility of CDAI and possibly SDAI in the routine assessment of disease activity in these RA patients and to document correlation of disease activity as measured with the above tools with the age, gender, modality of treatment, duration of symptoms and duration of disease.

Routine measurement of disease activity in clinical practice correlates with improved patient outcomes (independent of aggressive disease control). The commonly used disease activity measurement tool in RA is DAS-28. DAS-28 although currently considered the gold standard in RA disease activity assessment, is complex, expensive and time consuming. Although computation of the SDAI is simply a summation of its variables it still requires a laboratory parameter. CDAI on the other hand involves simple summation of its parameter and requires no laboratory parameter. In our set up many patients lack access to ESR or CRP due to many reasons and CDAI would be the best tool to use in daily clinical routine.

DAS-28 has proved to be in line with patients' thoughts about their disease and therefore the DAS-28 Categories

(DAS-28C) can be regarded as presenting the patients position¹², hence we felt justified in taking DAS-28C as the reference for comparison.

The total number of patients identified with RA over a period of 10 weeks was 107 which was slightly more than the numbers seen in previous studies¹³⁻¹⁵. This is a clear indication that there is an increase in number of patients with RA being seen in KNH. This increase is probably due to improvement in health awareness among the population, a better referral system and increasing urbanization.

The mean age of the study population was 48.7 years. Other studies done on this population had a similar mean age¹⁴⁻¹⁶. This can be attributed to the fact that RA has an onset between the 3rd and 5th decades of life. Female subjects represented 90% of the 104 subjects. This is also similar to what was found in previous studies on this population of patients¹⁴⁻¹⁶. We can attribute this to the fact that RA, like a majority of other connective tissue diseases affects females to a greater degree than males¹⁷. This was considerably higher than what has been the commonly reported ratio of 1:3. This could be due to the fact that we are seeing more RA patients and the health care seeking behavior is different in the two sexes.

In the treatment of RA most patients (86.5%) were on DMARDs. In 2007 only 46.7% of patients were on DMARDs¹⁵ and by 2012, this had risen to 75%¹⁴. Though encouraging since the current approach to treatment for patients with RA involves early initiation of aggressive therapy with DMARDs and biologic agents¹⁸, more than 13% of patients are not receiving the right treatment. Most of these were new patients i.e. diagnosed within 1 year and were yet to get or fill their DMARDs prescription. However, none of the patients in this study

were on a biologic agent. This is due to the prohibitive cost of these agents. The referral hospital is a public health care facility where patients pay out of pocket for all the services they receive in the clinic. Few have private health care insurance and even these are unable to cater for biologics. Over 60% of study participants were on a steroid. This high figure could be due to the fact that 13.5% of the study subjects were not on a DMARDS and majority of the study subjects had active disease.

Alpha, a measure of internal consistency was 0.67 for DAS-28, 0.69 for SDAI and 0.705 for CDAI showing the highest reliability for the test omitting acute phase reactants. Testing for agreement at the group level revealed, as expected, almost complete congruence between SDAI and CDAI (Spearman's Rank Correlation [ρ] = 0.989, $p < 0.001$). DAS-28 and SDAI as well as CDAI were also highly significantly correlated in this patient group ($\rho = 0.960$ for DAS-28/SDAI and $\rho = 0.892$ for DAS-28/CDAI; both $p < 0.001$). Kappa, a particularly individual measure used to estimate the relationship between disease activity categories as classified with the three tools was 0.78, $p < 0.001$ for the relationship between DAS-28 and SDAI when they classified disease as either controlled (remission and mild disease activity) or active (moderate and high disease activity). For the relationship between DAS-28 and CDAI for the same classification was 0.69, $p < 0.001$. This depicts substantial agreement of the tools in assigning disease activity scores of this patient group to the two categories.

For the assessment of the relationship where the four categories i.e. mild, moderate and high disease activity, plus the remission category, there was substantial agreement between DAS-28 and SDAI and between DAS-28 and CDAI in the moderate and high disease activity categories. However there was less than substantial agreement in the remission and mild disease activity categories in that DAS-28 classified more patients as being in remission as compared to SDAI and CDAI. This is because DAS-28 redistributes patient from the mild disease activity category to the remission category. The reason for this is that remission in RA has not been strictly defined. Although the DAS-28 level maybe indicating remission, mathematically 12 swollen joints can be present. However when applying SDAI and CDAI, the maximum joint count possible within remission range is 2 for both tender joint count and swollen joint count.

Our observations are in line with a large international study looking at disease activity and remission rates in 5848 RA patients in clinical practice from 24 countries with the highest remission rates when assessed according to DAS-28 (19.6%) and only 13.8% when assessed according to CDAI¹⁹.

A clinical trial involving more than 6600 RA patients receiving adalimumab open label for 12 weeks found 30% of the patients in remission according to the DAS-28, but only 24% and 27% according to SDAI and CDAI respectively²⁰.

There is an ongoing discussion to define remission more restrictively. A study done in Brazil in 2014 using different cut-off points for both DAS-28ESR and DAS-28CRP and comparing these to SDAI and CDAI categories showed improved agreement with lower cut-off points for DAS-28ESR and CRP²¹. The more stringent remission criteria by SDAI and CDAI may be of advantage in clinical practice for monitoring sustained remission. Not only is treatment as early as possible mandatory, but monitoring as close-matched as possible and also monitoring tools as accurate as possible very important. This seems to favor SDAI and CDAI for patient assessment. The highest internal consistency was with the CDAI, despite the fact that alpha increases with the increasing number of composite scale parameters. Thus CRP values add little to and contribute to the heterogeneity of a disease activity scale¹².

Full congruency between the three tools to assess RA patients cannot be expected because these instruments do not use exactly the same parameters. Also, different calculation methods are applied. This is also the reason why the weighting of the single items within the three composite scores is different²².

Existence of threshold values is necessary for categorizing patients. It facilitates documentation of disease status which helps in justifying expensive disease regimens in clinical routine. It is important to always use the same scoring system in an individual patient in routine clinical care¹². Current evidence does not recommend any tool as a gold standard for disease activity monitoring in RA²³.

The CDAI offers some advantages: first, remission is more stringently defined than with DAS-28 although no studies exist to show any long term differences between the patients classified as being in remission with CDAI and DAS-28. Second, lack of a laboratory test makes CDAI cheaper with potential to be used widely in resource poor settings. The primary requirement for efficient routine clinical work calls for easy and rapid organization of patient monitoring without losing reliability. Disease activity assessment tools should enable physicians to obtain reliable information about the disease course and should be sensitive enough to sound the alarm if deterioration occurs. The more easily applicable the assessment tool indexes are, the more they will be used by physicians. A simpler, affordable and uniform way of documenting a patient's disease will definitely result in improved RA patient care.

This study shows that assessment of disease activity with CDAI is comparable with DAS-28 in RA patients on follow-up in the KNH ROPC. CDAI was also more stringent in defining the lowest disease activity achievable i.e. remission.

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