Disease activity assessment of rheumatoid arthritis in daily practice: validity, internal consistency, reliability and congruency of the Disease Activity Score including 28 joints (DAS28) compared with the Clinical Disease Activity Index (CDAI)

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Abstract
Objectives
The Disease Activity Score including 28 joints (DAS28) and the Clinical Disease Activity Index (CDAI) were developed in order to provide a quantifiable measure of rheumatoid arthritis (RA) activity. The aim of this study was to evaluate the validity and internal consistency reliability for DAS28 and CDAI in patients with RA seen by rheumatologists in usual clinical care. We also compared proposed categories of high, moderate, and low activity and remission according to both scores.

Patients and methods
A sample of 2864 RA patients (2267 female, 597 male; mean age 58.5 yr, range 18-88 yr) were enrolled in this cross-sectional community-based study. Disease activity was assessed in each patient based on DAS28 and CDAI. Patients completed the Health Assessment Questionnaire (HAQ). Statistical evaluation was carried out by applying the Cronbach's values and principal component analysis (internal consistency reliability), the Pearson's coefficients, ANOVA and kappa statistic (convergent validity) and receiver operating characteristic (ROC) curve analysis (discriminant validity).

Results
Internal consistency testing of both scores indicated a reasonable difference, with Cronbach's alpha slightly higher for the DAS28. Interestingly, factor analysis revealed that the DAS28 constitutes a monocomponent measure in RA. Linear regression analysis showed a significant correlation between DAS28 and CDAI (p<0.0001). In addition, the DAS28 and CDAI were well correlated with HAQ (both at p level of <0.0001). The discriminatory power of both indices was good, without significant difference, but our results showed wide differences in both moderate/high disease activity and remission percentages (k=0.418).

Conclusions
DAS28 and CDAI are valid and simple acceptable ways to measure RA activity in the clinical practice, but disease activity categorized by these indices differ considerably. Further research is needed to resolve this issue.

Key words
Rheumatoid arthritis, disease activity, remission, DAS28, CDAI, validity, reliability.
Introduction

The Disease Activity Score (DAS) was developed in order to provide a quantifiable measure of rheumatoid arthritis (RA) activity (1). Its use is officially recommended by the European League Against Rheumatism (EULAR) to evaluate disease activity (2-4) and to identify patients whose therapy should be changed because of unacceptably high levels of DAS itself. This recommendation leads to the promotion of clinical practice that is strongly guided by DAS monitoring (5-9). Such an approach, in combination with monthly rheumatology consultation, has led to excellent outcomes in randomized controlled trials (10-12). This concept has also helped national rheumatology societies to define entry criteria for new biologic agents in terms of DAS (13-15).

In assessing patients with RA, reduced joint counts are as valid as the more comprehensive graded ones, since they preferentially includes joints that have the potential of improving with therapy (16). Using 28 tender and swollen joint counts, a modification of the original DAS index, DAS28, was developed and validated (1, 2, 17).

The Clinical Disease Activity Index (CDAI) is a new tool for the evaluation of disease activity in RA (18). It has been developed to provide physicians and patients with simple and more comprehensible instrument. In addition, the CDAI includes both the patient and the evaluator global assessments of disease activity, which adjusts for the frequently observed discrepancy between these two measures. Moreover, the CDAI is the only composite index that does not incorporate an acute phase response and it can therefore be always used to perform a disease activity evaluation (18). The CDAI has been validated in both a cross-sectional (routine) cohort and in an inception cohort (18-20).

In this study we evaluated the validity and internal consistency reliability for DAS28 and CDAI in 2864 patients with RA seen by rheumatologists in usual clinical care. We also compared proposed categories of high, moderate, and low activity and remission according to both scores.

Patients and methods

Patients

Data for this research was obtained as part of a community-based study in adult patients with RA as defined by the 1987 revised criteria of the American College of Rheumatology (formerly the American Rheumatism Association) (22). All patients gave their informed consent to be enrolled into this study according to the Declaration of Helsinki. The design of the study was approved by the local ethics committee. Briefly, the study was conducted from April to October 2004 on 2864 subjects aged 18 years and over, randomly selected from the lists of 186 rheumatologists. They were randomised among the about 1000 specialist referral in Italy, included both junior and senior rheumatologists (about 50% of each), and were representative of Italian rheumatologists, in terms of size of practice, geographical location, and socio-economic status. A number of them are actively involved in rheumatology training programs.

Clinical assessment

A comprehensive questionnaire including socio-demographic data and disease-related variables was administered to the patients. The socio-demographic variables were age, sex, body mass index (BMI), and highest attained level of education (primary; secondary; high school/university). Disease-related characteristics included disease duration (years since fulfilment of the classification criteria of RA), comorbidity, and the two measures for disease activity. Comorbidities included nine specific conditions (hypertension, myocardial infarction, lower extremity arterial disease, major neurologic problem, diabetes, gastrointestinal disease, chronic respiratory disease, kidney disease, and poor vision). Patients completed also the Italian version of the Health Assessment Questionnaire (HAQ) (23).

Although there is no official consensus as to what constitutes mild, moderate, or severe disability, HAQ scores were categorised into groups as follows: 0 – 0.49 (no disability), 0.50 – 0.99 (mild disability), 1.00 – 1.99 (moderate disability), and >2.00 (severe disability) (24). An additional question recorded...
on the examination sheet was the decision of the rheumatologist to initiate or change DMARD treatment. The rheumatologists were not informed that their decisions were part of the investigation. Disease activity was assessed in each patient (based on DAS28) and CDAI. The DAS28 range from 0 (totally inactive disease) to 9.4 (very active disease). The level of RA disease activity can be interpreted as low (DAS28≤3.2), moderate (3.2< DAS28≤5.1), or as high disease activity (DAS28 >5.1) (2–4). A DAS28<2.6 corresponds to remission, according to the ARA criteria (25). The CDAI range from 0 (totally inactive disease) to 76 (very active disease). Patients can be divided into those at low (CDAI ≤10), moderate (CDAI ≤22), and high disease activity (CDAI >22) (20, 25). A CDAI ≤2.8 corresponds to remission (20, 25).

Statistical analysis
Descriptive statistics are given as means, standard deviations (SD), and 95% confidence interval (CI) for the mean for continuous data or as per 95% confidence interval (CI) for the level of disease activity. We considered high in no internal consistency, to 1, indicating moderate (3.2< DAS28≤5.1), or as high disease activity (DAS28 >5.1) (2–4). A DAS28<2.6 corresponds to remission, according to the ARA criteria (25). The CDAI range from 0 (totally inactive disease) to 76 (very active disease). Patients can be divided into those at low (CDAI ≤10), moderate (CDAI ≤22), and high disease activity (CDAI >22) (20, 25). A CDAI ≤2.8 corresponds to remission (20, 25).

Results
Demographic and clinical data
For the large cross-sectional study (evaluation of disease activity), data of 2864 patients (mean age 58.5 yrs, range 18–88) with mean disease duration of 8.5 yrs (range 0.5–22 yrs) were utilized. 134 patients gave incomplete answers and were excluded from the study. A total of 2267 patients were female (median age 58.3 yrs, range 18–88); their mean disease duration was 9.1 yrs (range 0.5–22); 597 patients were male (mean age 59.3 yrs, range 18–86), with mean disease duration 8.0 yrs (range 0.5–21). 2135 of the 2864 patients (74.5%) were RF-positive (>40 IU/ml by nephelometry). The mean BMI was 24.8 kg/m². Body weight of the 2864 patients was as follows: (a) <60 kg, 842 patients (29.4%); (b) 60-100 kg, 1998 patients (69.8%) and (c) >100 kg, 24 patients (0.8%). The student t-test showed that women were more disabled (p<0.02), and less educated (p=0.032) than men. No significant differences were noted between female and male patients with respect to age and RF positivity; however, male patients had a shorter disease duration (p<0.005), which may be related to the higher mortality in men. Approximately, more than an half of patients reported at least one comorbidity with hypertension, heart diseases, gastrointestinal conditions, and chronic respiratory diseases being the most prevalent. Eighty-nine percent of patients were on disease modifying antirheumatic drugs (DMARDS), such as methotrexate (50%), antimalarials (27.6%), leflunomide (10.6%), sulfasalazine (6.9%), cyclosporin A (3.7%), or on a combination of methotrexate plus anti-TNF agent treatment (8.1%). A total of 1950 patients (68%) were taking corticosteroids (mean 3.8 mg prednisolone/day) and all patients received non-steroidal antirheumatic drugs, at least on demand. The mean values of the patients’ main demographic clinical characteristics are shown in Table I.
Table I. Demographic and clinical variables for the patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>95% CI</th>
<th>Median</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, in years</td>
<td>58.53</td>
<td>13.14</td>
<td>58.05 - 59.01</td>
<td>60.00</td>
<td>60.00 - 61.00</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.80</td>
<td>3.78</td>
<td>24.66 - 24.93</td>
<td>24.46</td>
<td>24.33 - 24.65</td>
</tr>
<tr>
<td>Tender joint count (0-28)</td>
<td>11.20</td>
<td>7.00</td>
<td>10.94 - 11.46</td>
<td>10.20</td>
<td>10.00 - 11.00</td>
</tr>
<tr>
<td>Swollen joint count (0-28)</td>
<td>7.92</td>
<td>6.00</td>
<td>7.70 - 8.14</td>
<td>7.00</td>
<td>7.00 - 7.00</td>
</tr>
<tr>
<td>Patient’s global assessment of activity (0-10)</td>
<td>4.83</td>
<td>6.06</td>
<td>4.60 - 5.053</td>
<td>4.50</td>
<td>4.40 - 4.70</td>
</tr>
<tr>
<td>Patient’s general health assessment (0-100)</td>
<td>46.88</td>
<td>23.93</td>
<td>46.00 - 47.76</td>
<td>44.50</td>
<td>43.00 - 46.00</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (normal &lt;20 mm)</td>
<td>4.37</td>
<td>2.19</td>
<td>4.29 - 4.45</td>
<td>4.00</td>
<td>4.00 - 4.30</td>
</tr>
<tr>
<td>Pain score</td>
<td>46.92</td>
<td>23.07</td>
<td>46.07 - 47.77</td>
<td>47.10</td>
<td>45.00 - 48.00</td>
</tr>
<tr>
<td>Health Assessment Questionnaire (0-3)</td>
<td>1.07</td>
<td>0.57</td>
<td>1.04 - 1.09</td>
<td>1.00</td>
<td>0.92 - 1.00</td>
</tr>
</tbody>
</table>

Distribution of DAS28 and CDAI scores

Table II summarizes the mean, SD, standard error of the mean (SEM), 95% CI for the mean, minimum, maximum, median values, 95% CI for the median, coefficient of skewness, and Kolmogorov-Smirnov test for the DAS28 and CDAI. Figure 1a-b presents estimates of central tendency and distributions for DAS28 and CDAI. The bar on the left of each graph represents the number of subjects with a score of 0 (floor effect); the bar on the right represents the number of subjects with a maximum possible score (ceiling effect). DAS28 and CDAI values in this cohort were normally distributed (Kolmogorov-Smirnov test), although the peak of CDAI was moderately shifted to the left (coefficient of skewness 0.171) compared with that of DAS28 that were negatively skewed (coefficient of skewness -0.086). The means (SD) of DAS28 and CDAI were 4.05 (1.28) and 28.55 (13.12), respectively (Table II).

Table II. Descriptive statistics for DAS28 and CDAI.

<table>
<thead>
<tr>
<th>Variable</th>
<th>DAS28 Mean</th>
<th>CDAI SD</th>
<th>95% CI Mean</th>
<th>Median</th>
<th>95% CI Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arithmetic mean</td>
<td>4.05</td>
<td>28.55</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard deviation</td>
<td>1.28</td>
<td>13.12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard error of the mean</td>
<td>0.02</td>
<td>0.23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI for the mean</td>
<td>4.00 to 4.09</td>
<td>28.04 to 29.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest value</td>
<td>0.24</td>
<td>0.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest value</td>
<td>8.09</td>
<td>66.90</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>4.12</td>
<td>28.50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI for the median</td>
<td>4.04 to 4.16</td>
<td>28.00 to 29.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coefficient of skewness</td>
<td>-0.086 (p=0.0597)</td>
<td>0.171 (p=0.0002)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kolmogorov-Smirnov test for normal distribution</td>
<td>accept normality (p=0.084)</td>
<td>accept normality (p=0.306)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Construct validity of the DAS28 and the CDAI

a) Internal consistency reliability and factor analysis. In testing for internal consistency reliability between composite indices of disease activity, we found that Cronbach’s alpha for the DAS28 was 0.719, indicating high reliability. In contrast, alpha was 0.532 in CDAI, indicating a reasonable difference in reliability and internal consistency for the two indices. Additionally, factor analysis revealed that the DAS28 constitutes a monocomponent measure in RA, while in CDAI two components could be seen to contribute to the total score (see Tables III and IV).

b) Convergent validity. Linear regression analysis showed a significant correlation between DAS28 and CDAI (R²=0.873; p<0.0001). In addition, the DAS28 and CDAI were well correlated with disability as measured by the HAQ (both at p level of <0.0001). The one-way analysis of variance (ANOVA), revealed DAS28 and CDAI’s ability to discriminate well between groups of patients in remission and high disease activity with different HAQ scores (both at p-level of <0.0001) (Figs. 2 A-B). The number of patients categorized by each criterion of disease activity, i.e. remission (DAS28≤2.6) and low disease activity criteria (DAS28≤5.1) included 297 (10.3%) and 394 (13.8%) patients, respectively, evaluated by DAS28, whereas there were 138 (4.8%) and 195 (6.8%) patients, respectively, by CDAI. On the other hand, patients categorized by moderate disease activity (DAS28≤5.1) and high disease activity criteria (DAS28>5.1) included 1451 (50.6%) and 802 (28%) patients, respectively by DAS28 criteria, whereas there were 686 (24%) and 1845 (64.4%) patients, respectively by CDAI criteria. To measure the level of overall agreement (defined as the percentage of observed exact agreements) of individual patient allocation into the different groups, the value of kappa was used. Analysis by kappa statistics showed moderate agreement between composite indices (kappa=0.418). No differences in age or disease duration between groups were found.

c) Discriminant validity. The ROC curves to discriminate between patients categorized by each criteria of disease activity, i.e. remission and/or low disease activity criteria and by moderate and/or high disease activity criteria in the 2 models with the DAS28 and CDAI indices were similar (Fig. 3). The discriminatory power of both indices was good, without significant difference, with an AUC of 0.904 (95% CI 0.893±0.915) for DAS28, and 0.899 (95% CI 0.877±0.901) for CDAI. From these data we calculated the cut-off
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value for remission/low disease activity with the highest combination of sensitivity and specificity. The resulting value for DAS28 was 5.14 (sensitivity 73.7%; specificity 96.4%), whereas the cut-off value for CDAI was 34.4 (sensitivity 75.8%; specificity 86.1%).

**Discussion**

Composite indices of disease activity such as the DAS28 are of great value in RA clinical trials and in daily clinical setting in the evaluation of treatment response. Recently, Vander Cruyssen et al. (28), comparing validity for the various disease activity indices, has suggested that the DAS28 is the best determinant of physician opinion, based on each physician’s decision to modify the dose of infliximab in patients with RA. Other indices are available to measure RA activity on a continuous scale; in particular, the Simplified Disease Activity Index (SDAI) (29) and, its modified version, the CDAI (18) score was simple to calculate and easy to use. In addition, the CDAI does not required an assessment of an acute-phase reactant and thus can be used to measure disease activity and response to treatment in any setting. Although the DAS28 and CDAI were found to have concurrent validity and were highly predictive of a change in therapy, differences were found when categorizing patients according to disease activity level (18, 28, 30).

![Fig. 1A. Overall histogram distribution of DAS28 values, including the normal distribution curve.](image1)

![Fig. 1B. Overall histogram distribution of CDAI values, including the normal distribution curve.](image2)

**Table III.** Item loading for the DAS28 based on 2864 RA patients*.

<table>
<thead>
<tr>
<th>DAS28</th>
<th>Component 1</th>
<th>Component 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tender joint count</td>
<td>0.846</td>
<td></td>
</tr>
<tr>
<td>Swollen joint count</td>
<td>0.854</td>
<td></td>
</tr>
<tr>
<td>Erythrocyte sedimentation</td>
<td>0.777</td>
<td></td>
</tr>
<tr>
<td>Patient’s general health</td>
<td>0.439</td>
<td></td>
</tr>
<tr>
<td>assessment</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

One principal component extracted. Extraction method: principal component analysis.

**Table IV.** Item loading for the CDAI based on 2864 RA patients*.

<table>
<thead>
<tr>
<th>CDAI</th>
<th>Component 1</th>
<th>Component 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tender joint count</td>
<td>0.905</td>
<td>-0.053</td>
</tr>
<tr>
<td>Swollen joint count</td>
<td>0.903</td>
<td>-0.034</td>
</tr>
<tr>
<td>Patient’s global assessment</td>
<td>-0.099</td>
<td>0.806</td>
</tr>
<tr>
<td>Evaluator’s global</td>
<td>0.139</td>
<td>0.753</td>
</tr>
<tr>
<td>assessment of activity</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Two principal component extracted. Extraction method: principal component analysis.

Our main objective was to assess this tool’s psychometric properties for judging disease activity in RA.

The metrics of CDAI shows, similarly to DAS28, that it is normally distributed. Internal consistency testing of both scores indicating a reasonable difference, with Cronbach’s alpha slightly higher for the DAS28. Factor analysis revealed that the DAS28 constitutes a monocomponent measure in RA, whereas the analysis revealed a two-factor solution for CDAI.

With respect to absolute values, the strong correlation between the CDAI and the DAS28, as described, was clearly reproducible (18, 20). Moreover, both scores were found to be highly correlated with HAQ. This finding is especially noteworthy because the HAQ is a functional measure, which is not based on or constructed with core set elements used in the DAS28 or CDAI. The correlation with the HAQ scores was very similar for the CDAI and the DAS28 in other studies (18,19), although the degrees of correlation varied considerably across the various cohorts (30). However, the
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Our data cannot evaluate which method is better, but results, in line with other reports, differ strikingly according to method (31, 32). The DAS28 cut points of remission, low, moderate, and high disease activity being designated in 10.3%, 13.8%, 50%, and 28% of patients, respectively, whereas same the CDAI cut points of being designated in 4.8%, 6.8%, 24%, and 64.4% of patients, respectively. Based on this results, the CDAI is the more stringent measure compared to the DAS28 when classifying patients in remission or with a minimal residual disease activity. The low stringency of the DAS28 remission criteria, especially in relation to residual joint counts, has already been addressed in previous studies (7, 18, 21, 33-35), and is also apparent from the difference proportion of patients in sustained remission in comparison with CDAI, suggesting a high frequency of “false positive remissions” using DAS28. Interestingly, Fransen et al. (24) found that the DAS performed better than the DAS28 in detecting remission. They found a greater area under the ROC curve for DAS than for DAS28 (both at their optimal cut off points) for detecting ACR remission, confirming DAS remission to be closer to the ACR than the DAS28 remission, and again suggesting lower residual joint counts in DAS remission than in DAS28 remission. Mierau et al. (34), and Kanna et al. (36) in observational studies, reported moderate agreement for DAS28 and CDAI when classifying patients in remission. Mierau et al. also reported residual swollen joints in 13% of patients in DAS28 remission compared to only 5% of patients in CDAI remission (34).

The CDAI activity categorizing was developed by experts’ opinions only, and not in comparison with the European League Against Rheumatism response criteria (EULARC), which may constitute the main reason for the discrepancies. The DAS28 was developed almost 2 decades ago (1) during an era with different medication options.

Fig. 2A. DAS28 scores compared with categorical rank in the HAQ. A generalized increase in the HAQ scores was observed for low, moderate, and high disease activity employing the DAS28.

Fig. 2B. CDAI scores compared with categorical rank in the HAQ. A generalized increase in the HAQ scores was observed for low, moderate, and high disease activity employing the CDAI.

Fig. 3. ROC curve of DAS28 and CDAI when used to discriminate the presence or absence of disease activity by the opinion of rheumatologist as external criterion. The curves plot the relationship between the sensitivity and 1–specificity of DAS28 and CDAI for different cut off levels of test positivity.
and treatment goals compared to the present one. This does not decrease the usefulness of the DAS28 index itself; it is a continuous measure of disease activity that can be used to set more ambitious treatment targets. However, we used those levels, recognizing that in the future the cut-off points of remission, low, moderate, and high disease activity may become lower because of more aggressive therapy of RA.

According to Soubrier et al. (37) we also tested here the accuracy of CDAI and DAS28 using the rheumatologist’s clinical decision to start (another) DMARD or change treatment as the gold standard. From Figure 3 it can be seen that the AUC of the ROC curve analysis was similar for the DAS28 (AUC=0.904) and for the CDAI (AUC=0.889). The resulting cut-off value for DAS28 was 5.1 (sensitivity 73.7%; specificity 96.4%), whereas the cut-off values for the CDAI was 34.1 (sensitivity 75.8%; specificity 86.1%). This disease activity cut-off value on the CDAI, is highly different from the >22 that had been established. In a similar analysis using the explicit judgment of the physicians with regard to moderate or high disease as the gold standard (ratings obtained from the survey mentioned above), Aletha et al. found similar results (20). In this study, the AUC of the DAS28 and CDAI followed closely behind, and were almost identical: 0.952 (0.940 to 0.963) and 0.949 (0.936 to 0.961), respectively. Another recent study showed a higher AUC for the DAS28 (AUC=0.840) than for the CDAI (AUC=0.821) (38). The gold standard in this investigation was the decision of the rheumatologist to increase the infliximab dose in patients on a particular clinical protocol, which served as a surrogate for insufficient control of the disease, i.e. moderate or high disease activity.

In summary, our study, shows that DAS28 and CDAI are valid and simple acceptable ways to measure RA activity in the clinical practice, but results showing wide differences in both moderate/high disease activity and remission percentages, indicate a need for a general consensus on cut-off criteria definitions.

Key messages
- DAS28 and CDAI are valid and reliable tools for RA disease activity measurement in clinical practice.
- Disease activity categorizing by these composite measures shows clearly significant discrepancies.

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