Classification of RA Into Active or Inactive With a Modified DAS, for Future Use as a Treat-to-target Tool, With a HandScan Score Replacing Joint Counts

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Abstract

Objectives

To establish the value of a modified DAS (DAS-OST) without joint counts but with a HandScan score (OST), versus that of DAS28, to classify RA as active versus inactive, with as reference standard the rheumatologist's clinical classification.

Methods

RA patients with at least one HandScan and DAS28 measurement performed at the same visit were included. Data was extracted from medical records, as was the clinical interpretation as active or inactive RA by the rheumatologist. Logistic regression analyses were performed to calculate areas under the receiver operating characteristics (AU-ROC) curves. The clinical interpretation was used as reference standard in all analyses, and disease activity measures were used as predictor variables. The performance of predictor variables (AU-ROCs) was compared.

Results

Data of 1505 unique RA patients were used for analyses. The highest AU-ROC of 0.88 (95%CI 0.85 – 0.90) was shown for DAS28; AU-ROC of DAS-OST was 0.78 (95%CI 0.75 – 0.81), difference 0.10, p<0.01.

Conclusions

Compared to DAS28, DAS-OST classified RA statistically significantly less well as active versus inactive, when using the clinical classification as reference standard. However, a DAS-modification without joint scores might have a place in strategies limiting routine outpatients’ visits to the rheumatologist.

Significant And/or Innovative Findings

- To classify RA as active versus inactive (i.e., based on rheumatologists’ clinical interpretation), the performance of DAS-OST was moderate and somewhat, but statistically significantly, inferior to that of DAS28.
- In a population with relative low disease activity as result of the treat-to-target principle, the additional value of DAS-OST (especially OST-score) in measuring disease activity is limited.
- A modified DAS without joint scores might have a place in novel strategies limiting routine outpatients’ visits to the rheumatologist.

Introduction

In rheumatoid arthritis (RA), life-long treatment according to the tight-control and treat-to-target principle is preferred, requiring frequent out-patient-clinic visits and contacts with rheumatologists.(1) Then, disease activity is usually assessed with DAS28,(2) a time consuming and partly subjective method.
Moreover, training/standardization of joint examinations, preferably yearly, is required to assess joints for swelling and tenderness as objectively as possible.\(^{3-6}\)

The HandScan is a medical device measuring inflammation in both hand and wrists using optical spectral transmission (OST, score 0 to 66 = worse). The OST-assessment takes about 1.5 minutes without much involvement of a healthcare worker.\(^{7}\) Some patients experience joint count assessments as painful, but the HandScan measurement is painless, an additional advantage.

Recently, to quickly assess disease activity in RA, using DAS28-ESR as reference, we developed and validated an index consisting of the OST-score, gender, erythrocyte sedimentation rate (ESR), and patients’ general health on a visual analogue scale (PGA-VAS). This modified DAS, with OST-score replacing joint counts, was named DAS-OST.\(^{8}\) Its formula is \(-0.44 + \text{OST-score} \times 0.03 + \text{male sex} \times -0.11 + \ln(\text{ESR}) \times 0.77 + \text{PGA-VAS} \times 0.03\), and its explained variance in the external validation cohort was 71\%, using DAS28-ESR as reference. To define remission (i.e., \(\text{DAS28} \leq 2.6\)) DAS-OST had an area under the receiver operating characteristic curve (AU-ROC) of 0.95(95\%CI 0.91–0.98); sensitivity was 79\%, specificity 92\%, and accuracy 88\%.

In the tight-control and treat-to-target principles, the decision whether RA is active or not is paramount. If there would be a tool to classify RA into active or inactive, the outpatients’ contacts with the rheumatologist might be limited to patients with active RA and/or medical problems.\(^{1}\)

The aim of this study was establishing the value of DAS-OST (i.e., modified DAS), versus that of DAS28, to classify RA as active versus inactive, with the rheumatologist’s clinical classification as active/inactive as reference standard, which is more comprehensive than a disease activity index alone.\(^{9}\) The clinical relevance would be that, if DAS-OST, that can be assessed without involvement of a rheumatologist, would validly classify RA into active or inactive, routine contacts of each individual patient with the rheumatologist might be less frequent in absence of active RA according to DAS-OST or other medical problems, thereby saving patients’ and rheumatologists’ time and/or costs.

**Methods**

This is a single center (Máxima MC Eindhoven; MMC) study, using routinely collected data from electronic medical records. The institutional ethical review board of MMC confirmed that the Medical Research Involving Human Subject Act (WMO) was not applicable to the protocol of this study (N19.002).

**Patients**

Detailed information on patients and obtained data has been reported elsewhere.\(^{8}\) For this study, a rheumatologist (AAAW) assessed the medical records for the treating rheumatologist’s clinical impressions on disease activity. Methods and results of the assessments for this clinical classification are provided in the online Supplementary file. In short, ‘active’ was characterized by initiation of a new disease modifying anti-rheumatic drug (DMARD), or an increase of the dose of current DMARD, or
intramuscular glucocorticoid injection, or the treating rheumatologist's notes indicating active disease, all at the consultation. 'Inactive' was characterized by tapering or stopping the current DMARD because of absence of disease activity (not because of adverse effects) or the treating rheumatologist's notes indicating inactive disease. A randomly drawn subset of 39 clinic visits assessed by AAAW was blindly reassessed by two other rheumatologists (JT and JWGJ); agreement on the clinical classification overall was 92.5%.

Statistical analyses

Continuous variables were described using means with standard deviations (SD) or medians with interquartile ranges (IQR), where appropriate. Frequencies and proportions were calculated for categorical variables.

DAS28 was plotted against DAS-OST in a scatter plot, and agreement of DAS28 with DAS-OST was tested using a random one-way intra correlation coefficient (ICC). The mean of the differences between DAS28 and DAS-OST was illustrated in a Bland-Altman plot.

The value DAS-OST and DAS28 to classify RA as active or inactive was established applying logistic regression analyses and calculating AU-ROC, using the rheumatologist's clinical classification as reference standard. Similar analyses were performed with OST-scores only, to evaluate the additional value of OST in DAS-OST. AU-ROCs were tested for statistically significant differences. For remission (≤ 2.6) and low disease activity (LDA, ≤ 3.2), for both DAS28 and DAS-OST, sensitivity, specificity, positive (PPV), negative predictive values (NPV) and accuracy were calculated. Youden's index was used to define optimal cut-offs for OST-scores, for inactive disease for males and females separately. Agreement between remission and LDA according to DAS28 and DAS-OST and the rheumatologist's clinical classification (reference standard) was tested using Cohen's kappa and Gwet's AC1.(10)

All tests were two-sided, a p-value ≤ 0.05 was considered as statistically significant. Analyses were performed in SAS version 9.4, NCSS version12.0.12, R version 3.6.2 with the package pROC 1.16.1, and AgreeStat version 2015.6.1.

Results

Patients

Data of 1505 unique RA patients was used. Patients' demographic and clinical data are shown in Table 1. Mean DAS28 and DAS-OST were both 2.5. Mean OST-score was somewhat higher in males than in females. According to clinical classification, RA of 79% of the patients was classified as inactive; 7 patients could not be clinically classified.
### Table 1

Patients’ demographics and clinical data

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients’ demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients, n (%)</td>
<td>1505 (100)</td>
<td>979 (65)</td>
<td>526 (35)</td>
</tr>
<tr>
<td>Age (year), mean (SD)</td>
<td>65.5 (12.1)</td>
<td>64.1 (12.7)</td>
<td>68.0 (10.6)</td>
</tr>
<tr>
<td>Duration of RA (year), mean (SD)</td>
<td>11.5 (8.3)</td>
<td>11.8 (8.3)</td>
<td>11.0 (8.5)</td>
</tr>
<tr>
<td>Seropositivity, n (%)</td>
<td>1068 (71)</td>
<td>691 (71)</td>
<td>377 (72)</td>
</tr>
<tr>
<td><strong>Clinical data</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>DAS28, mean (SD)</td>
<td>2.5 (1.3)</td>
<td>2.6 (1.2)</td>
<td>2.3 (1.3)</td>
</tr>
<tr>
<td>ESR (mm in 1st hour), median (IQR)</td>
<td>9.0 (5.0–21.0)</td>
<td>9.0 (5.0–21.0)</td>
<td>8.0 (2.0–19.0)</td>
</tr>
<tr>
<td>SJC28, median (IQR)</td>
<td>0 (0–2)</td>
<td>0 (0–2)</td>
<td>0 (0–2)</td>
</tr>
<tr>
<td>TJC28, median (IQR)</td>
<td>0 (0–1)</td>
<td>0 (0–2)</td>
<td>0 (0–1)</td>
</tr>
<tr>
<td>PGA-VAS global, median (IQR)</td>
<td>25.0 (10.0–50.0)</td>
<td>30.0 (10.0–50.0)</td>
<td>20.0 (10.0–43.0)</td>
</tr>
<tr>
<td>DAS-OST, mean (SD)</td>
<td>2.5 (1.2)</td>
<td>2.6 (1.2)</td>
<td>2.3 (1.2)</td>
</tr>
<tr>
<td>OST-score, mean (SD)</td>
<td>12.7 (5.3)</td>
<td>11.3 (4.7)</td>
<td>15.2 (5.3)</td>
</tr>
<tr>
<td><strong>Clinical classification, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Active</td>
<td>295 (20)</td>
<td>195 (20)</td>
<td>100 (19)</td>
</tr>
<tr>
<td>- Inactive</td>
<td>1203 (79)</td>
<td>781 (79)</td>
<td>422 (80)</td>
</tr>
<tr>
<td>- Not interpretable</td>
<td>7 (1)</td>
<td>3 (1)</td>
<td>4 (1)</td>
</tr>
</tbody>
</table>

SD = standard deviation, Seropositivity = presence of rheumatoid factor and/or anti-cyclic citrullinated peptide antibodies, IQR = interquartile range, DAS28 = disease activity score assessing 28 joints, ESR = erythrocyte sedimentation rate, SJC28 = swollen joint count assessing 28 joints, TJC28 = tender joint count assessing 28 joints, PGA-VAS = patients’ visual analogue scale of general health, range 0-100 = worst, DAS-OST = disease activity score using optical spectral transmission, OST = optical spectral transmission, range 0–66 = worst.

### Agreement

The relationship between DAS28 and DAS-OST is graphically shown in online Supplementary Figure S1; the ICC was 0.88 (95%CI 0.87–0.89). The mean difference between DAS28 and DAS-OST is shown in online Supplementary Figure S2.

### Discriminatory values
AU-ROC to classify RA patients as active/inactive for DAS28 was 0.88, 95%CI 0.85–0.90 and for DAS-OST and single OST-score, 0.78 (95%CI 0.75–0.81) and 0.59 (95%CI 0.55–0.63), respectively, Table 2. The discriminative ability was statistically significantly higher for DAS28, compared to DAS-OST: ∆AU-ROC 0.10, 95%CI 0.08–0.12, whereas it was statistically significantly higher for DAS-OST, compared to the OST-score: ∆AU-ROC 0.19, 95%CI 0.14–0.23, see Table 2 and Fig. 1.

Table 2

<table>
<thead>
<tr>
<th>ROC model</th>
<th>AU-ROC (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Individual model</strong></td>
<td></td>
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<tr>
<td>DAS28</td>
<td>0.88 (0.85–0.90)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>DAS-OST</td>
<td>0.78 (0.75–0.81)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>OST-score</td>
<td>0.59 (0.55–0.63)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td><strong>Comparisons</strong></td>
<td></td>
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<tr>
<td>Difference: DAS28 minus DAS-OST</td>
<td>0.10 (0.08–0.12)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Difference: DAS-OST minus OST-score</td>
<td>0.19 (0.14–0.23)</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

AU-ROC = Area under the receiver operating characteristics curve, CI = confidence interval, DAS28 = disease activity score assessing 28 joints, DAS-OST = disease activity using optical spectral transmission, OST-score = optical spectral transmission score.

For DAS28-based LDA classification, sensitivity and specificity were 87% and 72%, respectively and for DAS-OST-based LDA, these values were 81% and 59%, respectively, all versus the clinical reference. Lower values were obtained for both indices when using remission instead of LDA, see supplementary Table S1. Optimal cut-offs for inactive disease according OST-scores were ≤ 16.36 and ≤ 10.64 for males and females, respectively. Sensitivity and specificity for males were 66% and 50%, respectively, and 53% and 63%, respectively, for females, see supplementary Table S1. In line with the outcomes above, agreement (Cohen's kappa/Gwet's AC1) of the clinical classification with DAS28-based classification was higher compared with DAS-OST (0.41/0.55 and 0.54/0.76 vs. 0.24/0.37 and 0.36/0.64 for remission and LDA, respectively), see supplementary Table S1.

**Discussion**

To our knowledge this is the first study that identifies the value of a modified DAS with HandScan score replacing joint counts to classify RA as active versus inactive, with as reference standard the rheumatologist's clinical classification. DAS-OST showed a moderate performance (AU-ROC 0.78), but statistically significantly less, compared to DAS28. The performance of OST-score alone was poor, in line with earlier published data,(11) indicating that the OST-score has to be combined with other parameters.
into an index. However, in this setting, in which the study population had been treated according to the treat-to-target principle, resulting in relatively low disease activity (median SJC 0 and mean DAS28 2.5), also the contribution of the OST-score to DAS-OST was negligible.

Of course, in DAS-OST only joints of hand and wrist are included. The contribution of the OST-score probably would be higher in an RA-population with higher disease activity, e.g., starting DMARD-treatment, but this has to be investigated.

As expected, more favourable outcomes were obtained for DAS28-based LDA than for DAS-OST-based LDA. False negatives, as well as false positives were more often observed for DAS-OST than for DAS28 (4/20 vs. 2/20 and 2/20 vs. 1/20, respectively). Similarly, strength of agreement of the rheumatologist's classification with DAS28-based classification was moderate, and it was modest with DAS-OST. This limits the potential clinical applicability of DAS-OST. As a face-to-face visit with the rheumatologist is not required for DAS-OST, which saves time and cost, it would be efficient to select patients having no LDA based on DAS-OST for a face-to-face visit with the rheumatologist, assuming that most of those patients have active disease. In this setting, a higher specificity of DAS-OST (thus low number of patients with missed active RA) would be preferable over a high sensitivity, because at the visit, false classifications of RA as active can be corrected. Cost might also be saved when using DAS-OST compared to DAS28, as healthcare workers/ rheumatologists should be trained to perform joint count assessment as objective as possible. Of course, the HandScan device has to be purchased and operated.

The difference for males and females in optimal cut-off of OST-score for inactive disease is remarkable. Our previous study, as well as the current study show that OST-scores are systematically higher in males than in females. A plausible explanation is the difference in size and volume of hands between men and women, although we couldn't be clearly identified this.

A limitation of our study is that our reference, i.e., rheumatologist's clinical classification as active or inactive RA, probably is partly dependent of DAS28, as this measurement is widely applied in the Netherlands at out-patient-clinic visits. This could have favoured our study results regarding DAS28, but not regarding DAS-OST. The results of the OST-score only apply utilization of the HandScan in the setting of this study, e.g., categorizing disease as inactive or active in a population with relatively low disease activity.

Strength of our study is the relative large sample size of 1505 unique RA patients, with limited uninterpretable data.

**Conclusion**

Compared to DAS28, DAS-OST classified RA statistically significantly less well as active versus inactive, when using the clinical classification as reference standard. However, a DAS-modification without joint scores might have a place in strategies limiting routine outpatients’ visits to the rheumatologist.
Declarations

- Ethical Approval and Consent to participate

The institutional ethical review board of the Máxima MC confirmed that the Medical Research Involving Human Subjects Act (WMO) was not applicable to this study (N19.002), because no interventions or extra measurements were performed and only pseudonymized routinely collected data was extracted from medical records. As such patients did not give informed consent.

- Consent for publication

Not applicable.

- Availability of supporting data

Data may be obtained from a third party and are not publicly available.

- Competing interests

JMvL reports personal fees from Arxx Tx, Gesyntha, Magenta, Sanofi Genzyme, Leadiant, Boehringer-Ingelheim, Galapagos; grants and personal fees from Roche; grants from Astra Zeneca, MSD, Thermofisher; all outside the submitted work. MMAV, AAAW, JT, FPJGL, PMJW, JWGJ declare no competing of interests.

- Funding

The current study was not funded.

- Authors’ contributions

MMAV, AAAW, JWGJ contributed to study design, data cleaning and data analysis. All authors contributed to data interpretation and writing the manuscript, and approved the final version to be published and agree to the accountable for all aspects.

- Acknowledgements

None.

References


Figures
Figure 1

Title: Receiver operating characteristics curves with 95% confidence areas of sensitivity Legend: The classification as ‘not active disease’ according to the clinical interpretation was used as reference. DAS28 = disease activity score assessing 28 joints, DAS-OST = disease activity using optical spectral transmission, OST-score = optical spectral transmission score.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.
- OnlineSupplementaryfile.pdf