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Development and Validation of Rheumatoid Arthritis Disease Activity Indices Including HandScan (Optical Spectral Transmission) Scores

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Objective. To develop and validate a composite rheumatoid arthritis (RA) disease activity index using optical spectral transmission (OST) scores obtained with the HandScan, replacing tender and swollen joint counts.

Methods. RA patients from a single center routinely undergoing HandScan measurements with at least 1 concurrent OST score and Disease Activity Score in 28 joints (DAS28) were included. Data were extracted from medical records. Linear regression analyses with the DAS28 as the outcome were performed to create a disease activity index (DAS-OST). OST score, erythrocyte sedimentation rate (ESR), and patient global assessment (PtGA) visual analog scale (VAS), sex, age, disease duration, and rheumatoid factor status were evaluated as independent variables. Final models were derived based on the statistical significance of coefficients and model fit. Of the data, two-thirds were used for development and one-third for validation; external validation was performed in a cohort from another center. Agreement between DAS-OST and DAS28 was assessed using the Bland-Altman plot method and intraclass correlation coefficient (ICC). Diagnostic value of the DAS-OST was determined for established definitions of remission, low disease activity (LDA), and high disease activity (HDA).

Results. Data of 3,358 observations from 1,505 unique RA patients were extracted. DAS-OST was defined as: –0.44 + OST × 0.03 + male × –0.11 + LN(ESR) × 0.77 + PtGA VAS × 0.03. The ICCs between DAS-OST and DAS28 were 0.88 (95% confidence interval [95% CI] 0.87–0.90) and 0.82 (95% CI 0.75–0.86) and measurement errors were 0.58 and 0.87 in internal and external validation, respectively. Sensitivity for remission, LDA, and HDA was 79%, 91%, and 43%, respectively, and specificity was 92%, 80%, and 96% in external validation.

Conclusion. Using the HandScan, RA disease activity can be accurately estimated if combined with ESR, PtGA VAS, and sex into a disease activity index (DAS-OST).

INTRODUCTION

Rheumatoid arthritis (RA) is a common chronic inflammatory disease mainly affecting joints and surrounding tissues. The disease requires life-long treatment, preferably according to tight control and treat-to-target principles. Such treatment strategies require that patients frequently (in early disease or with active disease every 1–3 months) visit their physician for evaluation of medication effects, adverse events, and disease activity (1).

Disease activity is typically measured by a combination of parameters, including a swollen joint count in 28 joints (SJC28) and tender joint count in 28 joints (TJC28), C-reactive protein (CRP) level, or erythrocyte sedimentation rate (ESR) and a patient global assessment (PtGA) and/or physician assessment of disease activity or general health, typically using a visual analog scale

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SIGNIFICANCE & INNOVATIONS

- This is the first development of an RA disease activity index including optical spectral transmission (DAS-OST), replacing tender and swollen joints.
- The OST score (range 0–66) is obtained by a single HandScan measurement, which can be performed within ~1.5 minutes by a health care worker without a medical background.
- Applying the DAS-OST might save the rheumatologist the time needed to perform one of the usual disease activity assessments, including counts of the number of tender and swollen joints.
- With DAS-OST as an instrument monitoring patients' disease activity, strategies may be developed limiting patients' outpatient visits with their rheumatologist, if disease activity is low according to DAS-OST.

(VAS). These variables are often combined into an index like the Disease Activity Score in 28 joints (DAS28) (1).

However, this method of assessing disease activity is time consuming, especially given the busy out-patient clinics and limited time per patient that rheumatologists have nowadays. Also, to assess the joints for swelling and tenderness as objectively as possible, training and standardization of joint examinations is needed (2–4). Therefore a tool assessing disease activity quickly, easily, and objectively could be highly useful.

The HandScan is a device that measures within ~1.5 minutes inflammation of the wrist and small hand joints (i.e., metacarpophalangeal [MCP] 1–5, proximal interphalangeal [PIP] 1–5) using optical spectral transmission (OST) (5). Importantly, a HandScan measurement can be performed by a health care worker without a medical background (6). This procedure is more objective and less painful than assessment of joint counts. Detailed information is provided in Supplementary Appendix A, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24607.

The correlation between DAS28 and the OST score (range 0–66, where 66 = worst) is only moderate (7). This fact may not be surprising, as RA disease activity is a multifaceted construct. This correlation is reflected by the fact that PtGA VAS as well as CRP level/ESR are part of validated disease activity indices like DAS28, while the OST score is mainly a substitute of the SJC. In line with this fact, the correlation coefficient (ρ) of the OST score with SJC28 was found to be slightly higher (ρ = 0.50) than with DAS28 (ρ = 0.42) (7). Although the HandScan may be a substitution for joint count assessment only, this substitution may be beneficial, given its benefits, as described above. The current study aimed to develop and validate an index for assessing RA disease activity states using the OST score and other disease activity parameters, and to determine the agreement of this index with DAS28 and its accuracy in estimating remission, low disease activity (LDA), and high disease activity (HDA).

MATERIALS AND METHODS

This study used 2 cohorts. For model development and internal validation, routinely collected data from electronic medical records of the rheumatology department of Máxima Medical Center (MMC) Eindhoven were used, and for external validation, data from the ACURA Rheumatology Center Bad Kreuznach. The institutional ethical review board of MMC indicated that the Medical Research Involving Human Subjects Act was not applicable, as no interventions or extra measurements were performed and only pseudonymized routinely collected data were extracted from medical records. Therefore, patients did not give informed consent. The local standing committee for ethical conduct of Rhineland-Palatinate, Germany, approved the study of the ACURA cohort, and patients gave written informed consent.

Development and internal validation cohort. Patients with RA, visiting the outpatient clinic at MMC from April 2017 up to and including March 2019 were eligible for inclusion. Inclusion criteria were: 1) RA according to the American College of Rheumatology (ACR) 1987 or ACR/European Alliance of Associations for Rheumatology (EULAR) 2010 criteria (8); 2) no relevant visual deformations of hands or fingers (invalid HandScan measurement); 3) availability of a DAS28 measurement, with subsequent HandScan measurements, performed during the same clinical visit; 4) age >18 years; 5) no participation in interventional studies; and 6) DAS28 measurement performed without knowledge of the HandScan score.

External validation cohort. OST was performed in eligible RA patients during their stay in the ACURA inpatient clinic from September 2017 up to and including June 2018. All included patients met the 2010 ACR/EULAR classification criteria for RA (8). Patients age <18 years and with joint prostheses/implants, severe hand deformities, pronounced ulnar deviation, recent trauma or surgery, and known photosensitivity were excluded.

Assessments. Data of the DAS28 components (SJC28, TJC28, ESR, and PtGA VAS), age, sex, disease duration, rheumatoid factor (RF) status, and anti–cyclic citrullinated peptide (anti-CCP) status were extracted, if available. OST scores (i.e., total score and individual score of 22 joints) were obtained directly from the HandScan device. Data up to March 2019 were extracted. Data on the same variables were collected in the ACURA cohort. In both cohorts, DAS28 measures were assessed by a well-trained person, blinded with respect to the OST score. Inflammation markers, CRP level and/or ESR, were routinely tested and used for DAS28 calculation. RF and anti-CCP status were assessed by enzyme-linked immunosorbent assay.

Statistical analysis. *Model development.* Patient and disease characteristics were described using means ± SDs, medians with interquartile ranges, or frequencies with proportions, where appropriate. A random sample of two-thirds of the data from the MMC cohort was used as the development cohort. Using linear regression, we developed disease activity scores, including OST scores (DAS-OST). In these analyses, DAS28-ESR was used as a dependent variable (i.e., reference standard) and the OST score as independent variable. The association between OST score and DAS28 was assessed for linearity graphically as well using categorical values (defined by quartiles) and using quadratic transformations of the OST score. Covariates (i.e., ESR and PtGA VAS, and age, sex, disease duration, RF and/or anti-CCP status, which were deemed to possibly influence the OST score) were added to the model and removed one-by-one, retaining all variables that showed added predicted value beyond the OST score (as judged by a *P* value ≤0.20 or a decrease in adjusted R^2 upon removal). Finally, modification of the association between OST score and DAS28 by relevant covariates (i.e., those retained in the model) was evaluated, one-by-one, retaining interaction terms with a *P* value ≤0.20.

OST scores could be used as a total sum or expressed as a count of joints (JC) with inflammation (JC-OST: assessing 22 joints, MCP1–5, PIP1–5, and wrist, all bilaterally) as typically used in disease activity indices. Therefore, we developed a DAS-OST(JC) based on the JC-OST score. To define JC-OST, first a mixed-effects logistic regression analysis (mixed effects to account for clustering of joint scores within patients) using a random intercept was performed with joint swelling (yes/no, DAS28 component) as a dependent variable and the OST score of the corresponding individual joints, side (left/right), and joint type (MCP, PIP, wrist) as independent variables. This procedure was done to decide whether assuming 1 cutoff of the OST score for swelling is appropriate for every joint or whether specific cutoffs for a joint type and/or side are more appropriate. Optimal cutoffs were defined thereafter using Youden's index. In line with the square root transformation of SJC in DAS28, the square root of the JC-OST score was also used in developing the DAS-OST (JC). Further, a DAS-OST formula without PtGA VAS was developed (i.e., objective index) using the same methodology (9).

Model validation. Using the formula (and applying the derived OST score cutoffs for individual joints) as derived in the development cohort, DAS-OST was calculated in the internal validation cohort (i.e., the one-third of the MMC data not used for model development). External validation was performed in the ACURA cohort by applying the derived formula. Agreement between the different DAS-OST indices and DAS28 was determined in the internal and external validation cohorts by using the Bland-Altman plot method, calculating the SD of the difference (i.e., measurement error), and by random 2-way mixed-effects intraclass correlation coefficient (ICC) (10).

The receiver operating characteristic area under the curve (ROC AUC) was calculated to assess overall discrimination of DAS-OST for established definitions of remission, LDA, and HDA, based on DAS28 and Boolean (without PtGA VAS) remission criteria (i.e., SJC28 ≤1, TJC28 ≤1, PtGA VAS ≤10) and taking a CRP level ≤10 mg/liter, as estimated from the ESR (see Supplementary Appendix B, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24607) (11). Since ESR is routinely used in our population, CRP values were obtained only in special clinical circumstances. Therefore, directly calculating remission using the Boolean criteria was not

Table 1. Patient demographic and clinical data of the Máxima Medical Center (MMC) and ACURA cohort*

	MMC			
	Cohort	Cohort development	Internal validation	ACURA external validation
Demographic data				
Patients, no.	1,505	1,272	817	151
Female, no. (%)	979 (65)	831 (65)	541 (66)	100 (67)
Age, mean ± SD years	65.1 ± 12.0	64.9 ± 12.2	65.6 ± 11.6	60.5 ± 13.1
RA duration, mean ± SD years	11.4 ± 8.3	11.3 ± 8.4	11.7 ± 8.2	5.9 ± 8.0
Seropositivity, no. (%)	1,068 (71)	901 (72)	588 (73)	116 (77)
Clinical data				
Observations, no.	3,358	2,238	1,120	151
DAS28, mean ± SD	2.5 ± 1.3	2.5 ± 1.3	2.5 ± 1.2	3.8 ± 1.6
ESR, mm/hour	9 (5–21)	9 (5–21)	9 (5–21)	18 (10–34)
SJC28	0 (0–2)	0 (0–2)	0 (0–2)	1 (0–4)
TJC28	0 (0–2)	0 (0–2)	0 (0–2)	2 (0–8)
PtGA VAS	30 (10–50)	30 (10–50)	28 (10–50)	40 (20–65)
OST score, mean ± SD	12.6 ± 5.0	12.7 ± 5.1	12.6 ± 5.0	15.0 ± 6.1

* Values are the median (interquartile range) unless indicated otherwise. Seropositivity indicates the presence of rheumatoid factor and/or anti–cyclic citrullinated peptide antibodies. DAS28 = Disease Activity Score assessing 28 joints; ESR = erythrocyte sedimentation rate; OST = optical spectral transmission (range 0–66; 66 = worst); PtGA VAS = patient global assessment visual analog scale of patients' general health (range 0–100; 100 = worst); RA = rheumatoid arthritis; SJC28 = swollen joint count assessing 28 joints; TJC28 = tender joint count assessing 28 joints.

Table 2. Developed DAS-OST formulas using DAS28-ESR as reference*

Developed index	Formula	Explained variance of model (%)	Optimal cutoff for Boolean remission without PtGA VAS
DAS-OST	−0.44 + OST score × 0.03 + male sex × −0.11 + LN(ESR) × 0.77 + PtGA VAS × 0.03	78	2.2/2.7
DAS-OST(JC)	−0.34 + √JC-OST × 0.15 + male sex × −0.09 + LN(ESR) × 0.77 + PtGA VAS × 0.03	78	2.0/2.7
DAS-OST without PtGA VAS	−0.11 + OST score × 0.04 + male sex × −0.25 + LN(ESR) × 0.88	48	2.6†

* Formulas derived from development cohort (i.e., 2,238 observations from the Máxima Medical Center cohort). Disease Activity Score assessing 28 joints (DAS28) with erythrocyte sedimentation rate (ESR) was used as the reference in all models. JC = joint count, assessing 22 joints for inflammation, based on optical spectral transmission (OST); LN = log; PtGA VAS = patient global assessment by visual analog scale of general health.
† Boolean without PtGA VAS.

possible. We used ESR to estimate CRP level ≤10 mg/liter and then applied this estimate to calculate remission according to the Boolean criteria.

Furthermore, sensitivity, specificity, positive predictive value, and negative predictive value of DAS-OST for these established definitions were determined using the same cutoffs for DAS-OST as used for DAS28 (i.e., remission = DAS-OST ≤2.6, LDA = DAS-OST ≤3.2, and HDA = DAS-OST >5.1). For Boolean (without PtGA VAS) remission, a cutoff was predefined in the development cohort using Youden's index. All tests were 2-sided, and a *P* value less than or equal to 0.05 was considered statistically significant. No missing data were imputed, and analyses were performed in SAS, version 9.4.

RESULTS

Characteristics of the 2 patient cohorts. Data of 3,358 observations were extracted, without missing values, from the medical records of the MMC, including 1,505 unique RA patients. A random sample of two-thirds of the data (i.e., 2,238 observations) was used as a development cohort, and the remaining data (i.e., 1,120 observations) were used as an internal validation cohort. The external validation cohort included 168 unique RA patients. Due to missing values of the OST score and/or DAS28, data of 151 RA patients were used for the analyses. Patients' demographic and clinical data are shown in Table 1. Overall, disease activity (i.e., DAS28, its components, and the OST score) was statistically significantly higher in the ACURA cohort compared to the MMC cohorts, i.e., development and internal validation ($P < 0.01$ and $P < 0.01$, respectively, for all variables). Other statistically significant differences between the MMC cohorts and the ACURA cohort were shown for age, disease duration, and seropositivity ($P < 0.01$, $P < 0.01$, and $P < 0.01$, respectively, for all variables).

Model development. The derived formulas for the different DAS-OST indices are shown in Table 2. Next to ESR and PtGA VAS, sex was found to influence DAS28-ESR, independently from the OST score. None of the variables modified the association between OST score and DAS28. The model without PtGA VAS had a markedly lower explained variance (i.e., 48% versus 78% in models with PtGA VAS). The analysis on the association between joint-specific OST scores and the presence of swelling showed that establishing 1 cutoff for all joints was not possible, and therefore cutoffs were established per individual joint to calculate a JC-OST score (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24607). This JC-OST score was subsequently used to derive a DAS-OST(JC) formula, consisting of √JC-OST, sex, ESR, and PtGA-VAS (Table 2).

Model validation. *Agreement.* Table 3 shows agreement of the different DAS-OST indices with DAS28. In line with the results above, the DAS-OST including PtGA VAS showed higher agreement with the original DAS28-ESR compared to DAS-OST without PtGA VAS (ICC 0.88 and 0.82 in internal and external validation, respectively, versus 0.66 and 0.49), and the measurement error was larger with DAS-OST without PtGA VAS

Table 3. Agreement of DAS-OST indices with the DAS28 and measurement error in internal and external validation cohort*

Validation cohort, developed index	Measurement error	Agreement ICC (95% CI)
Internal		
DAS-OST	0.58	0.88 (0.87–0.90)
DAS-OST(JC)	0.58	0.88 (0.87–0.89)
DAS-OST without PtGA VAS	0.90	0.66 (0.62–0.69)
External		
DAS-OST	0.87	0.82 (0.75–0.86)
DAS-OST(JC)	0.87	0.81 (0.75–0.86)
DAS-OST without PtGA VAS	1.28	0.49 (0.36–0.60)

* Internal validation cohort consisted of 1,120 observations from the Máxima Medical Center cohort, not used in the development cohort. External validation cohort consisted of 151 observations from the ACURA cohort. The Disease Activity Score (DAS) with optical spectral transmission (DAS-OST) consisted of the total OST score, sex, erythrocyte sedimentation rate (ESR), and patient global assessment by visual analog scale of general health (PtGA VAS); DAS-OST(JC) consisted of √JC-OST, sex, ESR, and PtGA VAS; DAS-OST without PtGA VAS consisted of total OST score, sex, and ESR. 95% CI = 95% confidence interval; DAS28 = DAS assessing 28 joints; ICC = random 2-way mixed-effects intraclass correlation coefficient; JC = joint count.

Table 4. Diagnostic values of DAS-OST formula in internal and external validation cohort*

Validation cohort, disease activity state	ROC AUC	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy
Internal						
DAS-OST						
Remission	0.93	0.84 (0.81–0.86)	0.86 (0.83–0.89)	0.89 (0.87–0.92)	0.79 (0.76–0.83)	0.85
Boolean	0.87	0.83 (0.78–0.88)	0.70 (0.67–0.73)	0.41 (0.36–0.45)	0.94 (0.93–0.96)	0.73
Boolean without PtGA VAS	0.76	0.74 (0.71–0.77)	0.65 (0.61–0.69)	0.75 (0.72–0.79)	0.64 (0.59–0.68)	0.70
LDA	0.92	0.88 (0.86–0.90)	0.75 (0.70–0.80)	0.91 (0.89–0.93)	0.69 (0.64–0.74)	0.85
HDA	0.97	0.49 (0.33–0.65)	0.99 (0.99–1.00)	0.75 (0.58–0.92)	0.98 (0.97–0.99)	0.98
DAS-OST(JC)						
Remission	0.94	0.84 (0.82–0.87)	0.86 (0.83–0.89)	0.89 (0.87–0.92)	0.80 (0.76–0.83)	0.85
Boolean	0.86	0.75 (0.69–0.81)	0.77 (0.74–0.80)	0.45 (0.39–0.50)	0.93 (0.91–0.95)	0.77
Boolean without PtGA VAS	0.76	0.73 (0.70–0.77)	0.65 (0.61–0.69)	0.75 (0.72–0.78)	0.63 (0.59–0.67)	0.70
LDA	0.92	0.88 (0.86–0.90)	0.74 (0.69–0.79)	0.91 (0.89–0.93)	0.69 (0.64–0.74)	0.85
HDA	0.97	0.49 (0.33–0.65)	1.00 (0.99–1.00)	0.78 (0.61–0.95)	0.98 (0.97–0.99)	0.98
DAS-OST without PtGA VAS						
Remission	0.82	0.83 (0.80–0.86)	0.65 (0.61–0.70)	0.77 (0.74–0.80)	0.73 (0.69–0.77)	0.75
Boolean†	0.64	0.78 (0.72–0.83)	0.41 (0.38–0.45)	0.25 (0.21–0.28)	0.88 (0.85–0.91)	0.49
LDA	0.80	0.92 (0.91–0.94)	0.39 (0.33–0.45)	0.81 (0.79–0.84)	0.65 (0.58–0.72)	0.79
HDA	0.88	0.00 (0.00–0.00)	1.00 (1.00–1.00)	NA	0.97 (0.96–0.98)	0.97
External						
DAS-OST						
Remission	0.95	0.79 (0.67–0.91)	0.92 (0.86–0.97)	0.79 (0.67–0.91)	0.92 (0.86–0.97)	0.88
Boolean	–	–	–	–	–	–
Boolean without PtGA VAS	0.75	0.67 (0.36–0.97)	0.71 (0.64–0.78)	0.13 (0.03–0.22)	0.97 (0.94–1.00)	0.71
LDA	0.93	0.91 (0.84–0.99)	0.80 (0.72–0.88)	0.75 (0.65–0.85)	0.94 (0.88–0.99)	0.85
HDA	0.92	0.43 (0.26–0.59)	0.96 (0.93–1.00)	0.79 (0.61–0.97)	0.85 (0.78–0.91)	0.84
DAS-OST(JC)						
Remission	0.95	0.84 (0.73–0.95)	0.91 (0.84–0.95)	0.77 (0.64–0.89)	0.93 (0.88–0.98)	0.89
Boolean	–	–	–	–	–	–
Boolean without PtGA VAS	0.75	0.67 (0.36–0.97)	0.71 (0.64–0.78)	0.13 (0.03–0.22)	0.97 (0.94–1.00)	0.71
LDA	0.93	0.91 (0.84–0.99)	0.80 (0.72–0.89)	0.75 (0.65–0.85)	0.94 (0.88–0.99)	0.85
HDA	0.92	0.42 (0.26–0.58)	0.96 (0.93–1.00)	0.79 (0.61–0.97)	0.84 (0.78–0.90)	0.84
DAS-OST without PtGA VAS						
Remission	0.75	0.58 (0.43–0.73)	0.73 (0.64–0.81)	0.46 (0.33–0.60)	0.81 (0.73–0.89)	0.68
Boolean†	–	–	–	–	–	–
LDA	0.74	0.93 (0.87–1.00)	0.47 (0.37–0.58)	0.53 (0.43–0.63)	0.91 (0.84–0.99)	0.65
HDA	0.83	0.00 (0.00–0.00)	1.00 (1.00–1.00)	NA	0.77 (0.70–0.83)	0.77

* Internal validation cohort consisted of 1,120 observations from the Máxima Medical Center cohort, not used in the development cohort. External validation cohort consisted of 151 observations from the ACURA cohort. Disease Activity Score (DAS) using optical spectral transmission (DAS-OST) consisted of total OST score, sex, erythrocyte sedimentation rate (ESR), and patient global assessment by visual analog scale of general health (PtGA VAS); DAS-OST(JC) consisted of √JC-OST, sex, ESR, and PtGA VAS; DAS-OST without PtGA VAS consisted of total OST score, sex, and ESR. 95% CI = 95% confidence interval; DAS28 remission = DAS using 28 joints ≤2.6; HDA = high disease activity (DAS28 >5.1); JC = joint count; LDA = low disease activity (DAS28 ≤3.2); NA = not applicable; NPV = negative predictive value; PPV = positive predictive value; ROC AUC = receiver operating characteristic area under the curve.
† Boolean without PtGA VAS.

(in external validation 0.87 versus 1.28). Agreement and measurement error were similar, and the difference was not statistically significant for models using total OST score and JC-OST score to derive DAS-OST (Table 3 and Supplementary Figures 1–6, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24607).

Diagnostic value. Table 4 shows overall discrimination and diagnostic accuracy measures of DAS-OST indices for DAS28-based and Boolean remission, LDA, and HDA. Discriminatory ability for DAS-OST value was generally high, ranging from 0.86 to 0.97 for indices including PtGA VAS in internal validation, and from 0.92 to 0.95 in external validation, except for Boolean without PtGA VAS remission (ROC AUC 0.76 and 0.75, respectively). In line with agreement and measurement error results, ROC AUC and diagnostic accuracy measures of DAS-OST without PtGA VAS were lower.

Sensitivity and specificity for all disease states were good in general, but sensitivity for HDA was lower and 95% confidence intervals wider, compared to DAS28-based remission and LDA (Table 4). Using the DAS-OST without PtGA VAS cutoff, no patient was classified into the disease state HDA.

DISCUSSION

We developed and validated 3 disease activity indices using the OST score. DAS-OST(JC) performed similarly to DAS-OST, and therefore we prefer DAS-OST, as this index has the simplest formula. DAS-OST without PtGA VAS performed significantly less

well. In general, the diagnostic performance was found to be good, and results remained good in the external validation (ACURA) cohort, including patients with a more active disease compared to the outpatient clinic patients of the MMC cohort. The measurement error of DAS28 is generally assumed to be ~0.6 (12,13), and in the validation cohorts we found similar and slightly higher measurement errors between DAS28 and DAS-OST (12,13). Misclassification occurred in both cohorts, but mainly regarding the LDA and moderate disease activity categories and less regarding remission and HDA states (see Supplementary Tables 2 and 3, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24607).

The diagnostic performance of DAS-OST for defining specific disease activity states was in general good, although specifically, sensitivity for HDA was low, indicating that the performance in ruling out HDA using this index might be suboptimal (compared to the DAS28, the reference). However, the primary use would be detection of no remission and/or LDA, justifying intensification of the treatment strategy, and thus diagnostic accuracy for these outcomes is most important. Sensitivity and specificity for remission and LDA were adequate. Therefore we assume that a strategy applying our disease activity index, DAS-OST, might save the rheumatologists' time regarding evaluation of the disease activity of their patients in clinical practice, as a health care worker without medical background can perform a DAS-OST measurement, and only patients with no LDA/remission or health issues would typically require an additional or consecutive visit to the rheumatologist. Of course, any strategy with DAS-OST should be investigated before it would be implemented in daily practice, and to ensure quality of rheumatology care, a fixed appointment with the rheumatologist could be planned at least every 12 months. Possible implementation of DAS-OST would largely depend on the preferences of patients and rheumatologists and the flexibility of the outpatient clinics.

In contrast to other studies using imaging techniques (not the HandScan) as additional criteria in the management of RA (14), the OST score (as obtained by the HandScan imaging device) is integrated into a disease activity index, DAS-OST, replacing the joint count assessments. Therefore, we believe that using DAS-OST in the management of RA has a low risk of overtreatment, in contrast to studies when using imaging-based remission as an extra criterion. In addition, with DAS-OST, time and resources to train health care professionals to assess DAS28 are gained, as training is not required to assess DAS-OST.

For the current initial validation of DAS-OST, we used previously established and validated cutoffs for remission, LDA, and HDA based on the DAS28-ESR as used in clinical practice in participating centers. For future research it would be interesting to investigate different emerging cutoffs and disease activity definitions like those proposed by Fleischman et al (15).

A limitation of this study is the lack of information on smoking status, as smoking is known to decrease the blood flow of digits, which could influence the HandScan score (5). Furthermore, data were not available on body mass index and/or hand size, which have been found to affect the HandScan outcome (16). By including sex in our models, we may have partly corrected for the effect of hand size, which was found to influence the OST score independently from the disease activity variables in DAS-OST. Another limitation is that CRP level was estimated to calculate Boolean remission based on ESR, possibly influencing the diagnostic accuracy results compared to Boolean remission with assessed CRP level. As some biologic disease-modifying antirheumatic drugs (e.g., tocilizumab) are specifically known to influence CRP level more than ESR, this connection may have influenced the results. As specific information on medication use was lacking, the impact of this issue could not be established.

Despite these limitations, the current study containing information on 1,505 unique RA patients (with multiple observations) and an external validation cohort provided a unique opportunity to develop and validate a disease activity index using the HandScan. The fact that these were data of daily clinical practice of unselected patients enhances the generalizability of results.

Using the HandScan, RA disease activity states can be accurately estimated if OST scores are combined with ESR, PtGA VAS, and sex into a disease activity index (DAS-OST), which results in a quick and more objective disease activity index compared to joint count–based disease activity indices.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Verhoeven had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Verhoeven, Westgeest, Welsing.
Acquisition of data. Verhoeven, Westgeest, Triantafyllias, Welsing.
Analysis and interpretation of data. Verhoeven, Westgeest, Schwarting, Jacobs, Heller, van Laar, Lafeber, Tekstra, Triantafyllias, Welsing.

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