Psychometric properties of an index of three patient-reported outcome (PRO) measures, termed the CLinical ARthritis Activity (PRO-CLARA) in patients with rheumatoid arthritis. The NEW INDICES study

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Abstract

Objective

To evaluate the psychometric properties of an index based on 3 patient-reported outcome measures, termed PRO-CLinical ARthritis Activity (PRO-CLARA), in order to facilitate rapid and easy rheumatoid arthritis (RA) activity assessment in daily routine.

Methods

196 patients partially or not responding to disease modifying anti-rheumatic drugs (DMARDs), consented to participate in a multicentre cross-sectional study. For the evaluation of the psychometric properties of the PRO-CLARA, this population has been compared to another cohort of 247 outpatients with RA who were participating in a long-term observational study and who satisfying minimal disease activity and remission definitions. All patients completed the PRO-CLARA, combining patient's physical function, self-administered tender joint count and perception of global health status into a single measure of disease activity. Additional comparator composite indices were analysed. Internal consistency was assessed with Cronbach's alpha coefficient. A confirmatory factor analysis was carried out to test factor structure. Concurrent validity was analysed using Spearman's correlations and cross-tabulations. Discriminant validity to distinguish patients with active and non-active disease was assessed with receiver operating characteristic (ROC) curve analysis. For agreement analysis, kappa statistics were calculated.

Results

In testing for internal consistency, we found that Cronbach's alpha for the PRO-CLARA was 0.893, indicating high reliability. PRO-CLARA proved to be significantly correlated to established RA activity assessment tools. The area under ROC curve of the PRO-CLARA gives identical results to those provided by other comparator indices.

Conclusion

The study showed satisfactory psychometric properties of the PRO-CLARA.

Key words

Rheumatoid arthritis, PRO-CLARA, disease activity, patient-reported outcome, composite indices, validity, reliability

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Introduction

Rheumatoid arthritis (RA) is a chronic disabling inflammatory joint disease affecting about 0.5% of the population in Italy (1). The evaluation of the disease course requires comprehensive assessment of process and outcome (2). Because there is no gold standard of disease activity for RA, there are multiple measures needed to assess different aspects of underlying disease (3). A variety of instruments have been described and used for this purpose, including various types of joint counts, acute phase reactants, global assessment scales, pain, fatigue or physical status. However, due to the high variability of the presentation and course of RA, as well as the reflection of different disease characteristics in each of the above variable, no single measure can reliably capture disease activity in all patients; likewise, evaluation of all measures individually is associated with methodological and statistical problems, especially when employed as endpoints in clinical trials. All of these different considerations confer a rationale for "pooling" individual measures of disease activity into composite scores.

To integrate different aspects of disease activity and assess response to treatment, multiple different ways of defining response have been developed. These include dichotomous definitions (patient improved versus not improved) such as the American College of Rheumatology (ACR 20/50/70) criteria for improvement in RA (4), ordinal definitions (degree of response scored on an ordinal scale), continuous definitions (composite disease activity indices), and definitions that are hybrids of continuous and ordinal measures such as the ACR hybrid response measure (5) which utilises the established ACR core set measures. Continuous measures of disease activity include the Disease Activity Score (DAS) (6), the DAS using 28 joint counts (DAS-28) (7), the Simplified Disease Activity Index (SDAI) (8), the Clinical Disease Activity Index (CDAI) (9), and the Mean Overall Index for RA (MOI-RA) (10). All indices use a 28-swollen-joint count and a 28-tender-joint count, except for the original DAS which employs the Ritchie articular index (a graded assessment of 26 joint regions) (11) to evaluate tenderness and a 44-joint count to assess swelling. Acute phase reactants are integrated into the DAS (erythrocyte sedimentation rate [ESR]), DAS28 (ESR), SDAI (C-reactive protein [CRP]), and MOI-RA (ESR), but not into the CDAI. The inability to obtain ESR tests or to obtain them in a timely fashion so they could be used for clinical decision making was one of the reasons that the CDAI was developed. The European League Against Rheumatism response criteria (EULARC) are the current standard to monitor treatment response in RA clinical trials (12). "Tight control" according to DAS is associated with significantly better outcomes than usual non-quantitative care of RA (13-18). Achieving low disease activity, at best a remission-like state, is regarded as essential in improving prognosis (19, 20). Minimal disease activity of RA and remission can be assessed using definitions that are based on either DAS28 or the ACR core set criteria. All these composite disease activity indices include a formal joint count of tender and swollen joint performed by a physician/assessor. Traditionally, physicians or trained health care professionals assess joint count. However, joint counts are time-consuming and are generally performed only by trained clinicians participating in clinical trials (21, 22). Additionally, acute-phase reactants were shown to add little to those indices, as revealed by item-weighting analyses (9). A potential alternative is patient self-assessment. This is advantageous in clinical practice settings with limited resources and in epidemiological research such as longitudinal studies (23). Data from patients concerning only the three ACR Core Data Set patient-reported outcome (PRO) measures – physical function, pain and global health status (24, 25) – appear adequate to document disease activity and monitor effectiveness of therapies in patients with RA (26). PROs are an attractive option in a busy medical practice, as the time burden is transferred from the clinician to the patient. The validity and usefulness of PRO data in evaluating and monitoring patients RA have been well document-

ed (27-29). Further, composite disease activity indices of only PRO measures have been proposed, including the RA disease activity index (RADAI) (30) and its short-form (31) or the newly adapted RADAI-5 (32), the patients activity scale (PAS) or PAS-II (29), and routine assessment of patient index data (RAPID3) (33, 34). The RAPID3 has been shown to be as efficient as DAS and CDAI to detect changes in clinical trials (26, 33), and to be correlated with DAS and CDAI in usual clinical settings (35). These instruments are easier to administer and less expensive than physician-observed disease activity and process measures.

In this study we aimed to assess the psychometric properties of a new composite instrument termed CLinical ARthritis Activity (PRO-CLARA) that uses only three PRO measures. We hypothesised that this index would facilitate rapid and easy RA activity assessment in daily routine. We also analysed additional CLARA scores, which included a swollen joint count by a physician/assessor, to assess whether inclusion of these data might provide a substantially more informative index than PRO-CLARA.

Patients and methods

Patients

One hundred and ninety six patients with moderate to severe RA from 27 rheumatologic centres in Italy consented to participate in a multicentre cross-sectional study of RA cohort, termed the NEW INDICES study. These subjects, partial- or non-responders to disease modifying anti-rheumatic drugs (DMARDs), were candidates to start a TNF-inhibitor. The involved rheumatologists were instructed to collect the data following standard definitions and procedures. Data on current and previous treatments were collected from the medical records and confirmed by the patients during the clinical visits. The patient selection criteria were fulfilment of the ACR 1987 revised criteria for RA (36), age 18-75 years, and active disease defined by at least three of the following: either ESR ≥28 mm/hour or CRP >19 mg/dl, morning stiffness ≥30 minutes, more than five swollen joints, and more than ten tender joints (37). The protocol was approved by the national health authorities and ethics committees in all 27 participating hospitals. All the patients gave informed written consent.

For the evaluation of the psychometric properties of the PRO-CLARA, the above described population (Group A) has been compared to another cohort of 247 outpatients with RA (Group B), enrolled in a long-term observational study conducted by the Clinical Rheumatology of the Università Politecnica delle Marche, Ancona, Italy. This population included subjects with the following characteristics: 80.1% female, age 58.1±11.2 years, disease duration 6.2±6.6 years, and satisfaction of minimal disease activity (MDA) and remission definitions while taking conventional DMARDs (*i.e.* methotrexate, sulfasalazine, leflunomide, antimalarials), or tumour necrosis factor-α blockers (*i.e.* infliximab, etanercept and adalimumab); 185 patients (62%) were taking corticosteroids (mean 3.35 mg prednisolone/day, range 2.5–25 mg). MDA definitions included at least 5 of the following 7 World Health Organization (WHO)/International League of Associations for Rheumatology (ILAR) core set measure thresholds (38), as proposed by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) (39): VAS pain ≤2 (0–10), swollen joint count (SJC) ≤1 (out of 28), tender joint count (TJC) ≤1 (out of 28), Health Assessment Questionnaire (HAQ) ≤0.5 (0–3), physician global assessment ≤1.5 (0–10), patient global assessment ≤2 (0–10), and ESR ≤20 mm/hour. Remission was evaluated according to modified ACR (*m*ACR). Fulfilment of the mACR remission criteria required 4 of the following 5 items to be met: morning stiffness ≤15 minutes, no joint pain by history, no joint tenderness, no swollen joints, and ESR<30 mm (female) or <20 mm (male). These thresholds were comparable to the original Pinals criteria (40), but with fatigue omitted (41). The other 4 criteria had to be fulfilled at one point in time (42). All these 247 patients (Group B) were evaluated as controls for the NEW INDICES study.

Functional measures

All patients completed the Recent-Onset Arthritis Disability (ROAD) (43, 44) and the Health Assessment Questionnaire (HAQ) (45).

The ROAD questionnaire is a reliable, valid and responsive tool for measuring physical functioning in patients with RA, and it is suitable for use in clinical trials and daily clinical practice (43, 44). The ROAD consists of 12 items assessing a patient's level of functional ability and includes questions related to fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both upper and lower extremities. For each item, patients are asked to rate level of difficulty over the past week on a 5-point scale, which ranges from 0 (without any difficulty) to 4 (unable to do). The ROAD score ranges from 0 to 48. In order to express these scores in a more clinically meaningful format, a simple mathematical normalisation procedure was then performed so that all the scores could be expressed in the range 0-10, with 0 representing best status and 10 representing poorest status. Unlike the HAQ, the ROAD can be scored in 15 to 20 seconds.

The HAQ assesses the degree of difficulty a person has in accomplishing tasks in 8 functional areas: dressing and grooming, arising, eating, walking, hygiene, reach, grip, activities (45). For each item, patients are asked to rate level of difficulty over the past week on a 4-point scale, which ranges from 0 (no difficulty) to 3 (unable to perform). To calculate the disability dimension score, a score is disability score ranges from 0 to 3, with a higher score indicating more disability. The HAQ is calculated for each of the subscales; subscales are then summed and the sum divided by 8. A version adapted for use among Italian patients was utilised in the present study (46).

Composite disease activity indices

Clinical assessments comprised the following single items of disease activity: 28-joint counts for swollen and tender joints (SJC and TJC, respectively), patient self-administered tender joint count (TJC), pain numerical rating

scale (NRS-pain), evaluator and patient assessments of disease activity (EGA, PGA, respectively) by NRS, patient assessment of general status (GH), physical disability (by HAQ and ROAD questionnaires) (43-46), morning stiffness, ESR and CRP. These variables were used to calculate fulfilment of the MDA and mACR remission criteria and all composite disease activity indices. Consensus concerning joint assessment was met to avoid high inter-rater variabilities among the physicians.

Methods to assess CLARA scores

The PRO-CLARA is a short and easy to complete self-administered index, without formal joint counts, combining three items on patient's physical function (as measured by ROAD) (43, 44), self-administered TJC and PGA into a single measure of disease activity. The self-administered TJC was evaluated according to joint list of the RADAI (30). The RADAI joint mannequin list queries pain "today" in 16 joints or joint groups, including left and right shoulders, elbows, wrists, fingers, hips, knees, ankles, and toes. The self-administered TJC weighted the degree of tenderness of each joint on the following scale: 0 = none; 1 = mild; 2 = moderate; 3 = severe. The self-administered TJC is scored as 0–48; the raw 0–48 score may be recoded to 0–10 using the scoring template in Fig. 1. The PGA, is scored 0–10 on an 11-point NRS, with the follow question: "How would you describe your general health today? (0 = very well to 10 = very poorly)". The total score of the PRO-CLARA was completed by summing the scores of the three individual measures and dividing this by three, and range from 0 to 10. Template to score PRO-CLARA is available in Fig. 1. CLARA adds to ROAD and self-administered TJC a standard 28-SJC, performed by a physician/assessor. To calculate CLARA, the 28-joint count is scored 0–28, recoded to a 0–10 scale, then added to self-administered TJC and ROAD for a total of 0–30, and finally divided by 3 to give an adjusted 0–10 score. Each of 3 measures included in a PRO-CLARA and CLARA scores is weighted equally on a 0–10 scale, in contrast to ACR improvement criteria, DAS28, SDAI and CDAI, in which joint-count data are weighted more heavily than other Core Set measures. Adjustment of all PRO-CLARA and CLARA scores to 0–10 facilitates simple comparisons of index to one another and to DAS28, SDAI, and CDAI.

Methods to assess the other composite indices

The DAS28 includes 28-SJC and 28-TJC in addition to GH scale (0-100) and ESR values (7). The DAS28 was calculated by entering these four variables into the WEB calculator, which was obtained from http://www.das-score.nl/www.das-score.nl/index.htm. 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) (ref needed). A DAS28 <2.6 corresponds to remission, according to the OMERACT criteria (12). The SDAI (8) and the CDAI (9) are two new tools for the evaluation of disease activity in RA. They have been developed to provide physicians and patients with simple and more comprehensible instruments. Moreover, the CDAI is the only composite index that does not incorporate an acute phase response and can, therefore, be used to conduct a disease activity evaluation essentially anytime and anywhere. The SDAI employs a linear sum of five untransformed, unweighted variables, including 28-SJC and 28-TJC, PGA and EGA on an 11–point NRS, and CRP. The SDAI score is computed as follow: SDAI = [SJC + TJC + PGA (in cm) + EGA (in cm) + CRP (in mg/dl)]. The range of SDAI is 0-86. Predefined thresholds for remission, low and moderate levels of disease activity are 3.3, 11 and 26, respectively (47). The CDAI is a modification of the SDAI without laboratory evaluation (CRP) to allow immediate clinical assessment. The CDAI score is computed as follow: CDAI = SJC + TJC + PGA (in cm) + EGA (in cm). Range of CDAI is 0-76. Thresholds for separating remission, low and moderate levels of disease activity are at 2.8, 10 and 22, respectively (48).

The MOI-RA is the mean of standardised values of 28-SJC and 28-TJC, EGA and PGA, (NSR 0-100), pain (NSR 0-100), the HAQ, and ESR (1-100). In ESR, all values above 100 are replaced by value 100. HAQ value (range 0-3) is divided by its maximum, which is 3, and multiplied by 100. Similar calculations are performed with the other components: they are standardised to range from 0 to 100. The range of MOI-RA is 0-100, with higher values indicate poorer outcomes (10).

The RADAI is a modification of the questionnaire introduced by Mason et al. (49). The goal of the RADAI is to provide an easy to use assessment of RA disease activity, which serves as a complement to the physician's, assessments and by which the physician's assessment in certain situations could be omitted, especially in observational studies or situations wherein patient management may not be possible or where it may be too demanding (30). The RADAI contains five items on global disease activity during the past 6 months, current disease activity as measured by swollen and tender joints, current amount of arthritis pain, current duration of morning stiffness and current number of tender joints in a joint list. The first three items are scored on an 11-point NRS, with verbal anchors from "no disease activity"/"no pain" (score 0) to "extreme disease activity"/ "extreme pain" (score 10). The last two items are scored on a seven-point and four-point verbal rating scale. The scores on these two items range from 0 to 6 and from 0 to 48, and were transformed to a 0–10 scale, with higher scores indicating more disease activity. The total score of the RADAI was computed by summing the scores of the individual non-missing items and dividing this by five, and ranges from 0 to 10. The RADAI has primarily been developed for use in clinical and epidemiological studies where clinical assessments are not available or too demanding (30). Nevertheless, the RADAI may also be useful in clinical practice and in clinical trials (31).

The routine assessment of patient index data 3 (RAPID3) is an index of only three PRO measures – physical

CLINICAL ARTHRITIS ACTIVITY (PRO-CLARA) index

Please try to answer each question, even if you do not think it is related to you.
There are no right or wrong answers. Please answer exactly as you think or feel. Thank you.

A) Please check (√) the ONE best answer for your abilities:

OVER THE LAST WEEK, were you able to:	Without **ANY** difficulty	With **A LITTLE** of difficulty	With **SOME** difficulty	With **MUCH** difficulty	**UNABLE** to do
1. Close your hand completely?	❒ 0	❒ 1	❒ 2	❒ 3	❒ 4
2. Accept a hand shake?	❒ 0	❒ 1	❒ 2	❒ 3	❒ 4
3. Do up buttons?	❒ 0	❒ 1	❒ 2	❒ 3	❒ 4
4. Open jars which have been previously opened?	❒ 0	❒ 1	❒ 2	❒ 3	❒ 4
5. Reach up and take down a 2 Kg object from above your head?	❒ 0	❒ 1	❒ 2	❒ 3	❒ 4
6. Stand up?	❒ 0	❒ 1	❒ 2	❒ 3	❒ 4
7. Walk on a flat ground?	❒ 0	❒ 1	❒ 2	❒ 3	❒ 4
8. Climb up five steps or stairs?	❒ 0	❒ 1	❒ 2	❒ 3	❒ 4
9. Get into and out of a car?	❒ 0	❒ 1	❒ 2	❒ 3	❒ 4
10. Get into and out of a car?	❒ 0	❒ 1	❒ 2	❒ 3	❒ 4
11. Wash and dry your body?	❒ 0	❒ 1	❒ 2	❒ 3	❒ 4
12. Are you still able to work at home or/and on your job?	❒ 0	❒ 1	❒ 2	❒ 3	❒ 4

B) Please place a check (√) in the appropriate spot to indicate the amount of pain you are having today in each of the joint areas listed below:

LEFT	**None**	**Mild**	**Moderate**	**Severe**	***RIGHT***	**None**	**Mild**	**Moderate**	**Severe**
Hand	❒ 0	❒ 1	❒ 2	❒ 3	Hand	❒ 0	❒ 1	❒ 2	❒ 3
Wrist	❒ 0	❒ 1	❒ 2	❒ 3	Wrist	❒ 0	❒ 1	❒ 2	❒ 3
Elbow	❒ 0	❒ 1	❒ 2	❒ 3	Elbow	❒ 0	❒ 1	❒ 2	❒ 3
Shoulder	❒ 0	❒ 1	❒ 2	❒ 3	Shoulder	❒ 0	❒ 1	❒ 2	❒ 3
Hip	❒ 0	❒ 1	❒ 2	❒ 3	Hip	❒ 0	❒ 1	❒ 2	❒ 3
Knee	❒ 0	❒ 1	❒ 2	❒ 3	Knee	❒ 0	❒ 1	❒ 2	❒ 3
Ankle	❒ 0	❒ 1	❒ 2	❒ 3	Ankle	❒ 0	❒ 1	❒ 2	❒ 3
Foot	❒ 0	❒ 1	❒ 2	❒ 3	Foot	❒ 0	❒ 1	❒ 2	❒ 3

ROAD ☐

SELF-TJC ☐

FOR OFFICE USE ONLY

1=0.2	2=0.4	3=0.6	4=0.8	5=1.0	6=1.3	7=1.5	8=1.7	9=1.9	10=2.1	11=2.3	12=2.5
13=2.7	14=2.9	15=3.1	16=3.3	17=3.5	18=3.8	19=4.0	20=4.2	21=4.4	22=4.6	23=4.8	24=5.0
25=5.2	26=5.4	27=5.6	28=5.8	29=6.0	30=6.3	31=6.5	32=6.7	33=6.9	34=7.1	35=7.3	36=7.5
37=7.7	38=7.9	39=8.1	40=8.3	41=8.5	42=8.8	43=9.0	44=9.2	45=9.4	46=9.6	47=9.8	48=10

C) Please place a check (√) in the appropriate numerical scale to indicate how would you describe your general health today:

Very well	0	1	2	3	4	5	6	7	8	9	10	**Very poorly**

Fig. 1. The Patient Reported Outcomes-CLinical Arthritis Activity (PRO-CLARA) includes 12 items of the Recent Onset Arthritis Disability (ROAD) questionnaire to assess physical function, self-administered tender joint count, and patient global estimate. The 12 ROAD items are each scored on a 5-point scale, which ranges from 0 (without any difficulty) to 4 (unable to do). The self-administered TJC weighted the degree of tenderness of each joint on the following scale: 0=none; 1=mild; 2=moderate; 3=severe. The self-administered TJC is scored as 0–48. Both raw 0-48 scores are recoded as 0-10 using a scoring template on the bottom of the page. The perception of global health status is scored 0-10 on a 11 points NRS. The three 0–10 scores are added together for a raw score of 0–30, and divided by 3 to give an adjusted 0–10 score.

function, pain and patient global assessment (PGA) – designed for usual clinical care, although they also may be used for clinical research. The Core Data Set measures on the multidimensional HAQ (MDHAQ) for function (FN), pain and PGA, are each scored 0-10 and recoded on the MDHAQ. The raw total score of 0-30 may be recoded to 0-10 using a scoring template (50,51). Proposed severity (rather than activity) categories for RAPID3 are: >4 = high, 2.01–4 = moderate, 1.01–2 = low, and ≤_1 = near-remission on an adjusted 0–10 scale. On an unadjusted 0–30 scale, the severity categories are defined as >12 = high, 6.01–12 = moderate, 3.01–6 = lower, and ≤3 = near-remission (34).

Statistical analysis

Continuous data were presented as means with standard deviations (SDs) or medians with 95% confidence interval (95% CI), depending on the distribution of the data (tested with the Kolmogorov-Smirnov test). Categorical data were presented as proportions. Demographic and clinical measures were compared using Mann-Whitney U test or Kruskal-Wallis test for continuous variables, and chi-square analysis for discontinuous variables. *P*-values below 0.05 were regarded as statistically significant. Following standard guidelines for the evaluation of measurement properties of quality of life instruments (52), we tested the feasibility, construct validity and reliability of the indices. The operational qualities or feasibility of the PRO-CLARA index were analysed according to the percentage of patients who were able to interpret the items and complete the index by themselves and by the time employed in filling it out. The PRO-CLARA was administered to a group of 77 RA patients (57 women and 20 men) aged from 20 to 78 (mean 55.8 years) not previously involved in the development of the tool. To examine participants' level of comprehension of the instruments' content, a proxy question was asked, "did you have any difficulty understanding the questionnaire items?" (to be answered on a five-point Likert scale). The clinical construct validity of the PRO-CLARA was examined in three ways. First, we explored the underlying component structure of the items. As an indicator of internal consistency reliability, we calculated Cronbach's values. Achievable values for Cronbach's range from 0, indicating no internal consistency, to 1, indicating identical results. According to Nunnally, a value of 0.80 is sufficient for research purposes and a value of 0.90 is recommended when individual decisions are made based on specific test scores (53). In addition, item weighting was assessed by confirmatory factor analysis, using principal axis extraction with the varimax rotation method, an approach that maximises the independence of the factors. An eigenvalue criterion of 1.0 was used to select the factors, and the results are given in terms of the percentage of variance in the scale score explained by the principal factor. The criterion of an eigenvalues greater than 1 was proposed by Kaiser for principal component analysis (54). Secondly, we examined convergent validity by correlating disease activity measures with each other. Next, we used the HAQ score as an additional external comparator in the correlation analysis with these indices. The Spearman's coefficient of rank correlation (rho) was used for analysing correlations. Correlations >0.90 were interpreted as very high, 0.70–0.89 as high, 0.50–0.69 as moderate, 0.26–0.49 as low and ≤0.25 as little if any correlation (55). To show relationship between measures, scatter plots with linear regression line were drawn. We next investigated the agreement of the different activity scores in individual patients. We, therefore, created patient groups based on the patients' physical disability ranks within the cohort. Although there is no official consensus as to what constitutes mild, moderate, or severe disability, HAQ scores were categorised into 4 groups as follows: 0 to 0.49 (no disability), 0.50–0.99 (mild disability), 1.00–1.99 (moderate disability), and >2.00 (severe disability) (41). We further explored the discriminative accuracy of the CLARA and PRO-CLARA scores. To distinguish patients with active (Group A) and non-active disease (Group B) and to assess their respective cut off points values, the receiver operating characteristic (ROC) curve analysis was used. The OMERACT criteria for MDA and mACR criteria for remission were applied as external criterion. Since ROC analysis requires external criteria to be dichotomous, MDA and *m*ACR remission were grouped together as "overall" low disease activity. ROC curves were created by plotting the true-positive proportion (sensitivity) versus the false-positive proportion (100-specificity) for the discrimination between inactive and active patients for multiple cut-off points. The area under the ROC curve (AUC) was calculated to quantify the discriminative accuracy. According to Swets *et al*. (56), AUC from 0.50 to about 0.70 represent poor accuracy, those from 0.70 and 0.90 are "useful for some purposes", and higher values represent high accuracy. From the ROC curves, we computed the optimal cut off point corresponding to the maximum sum of sensitivity and specificity. The non-parametric Wilcoxon's signed ranks test is used for calculation and comparison of the areas under the ROC curves, as suggested by Hanley and McNeil (57). All data were entered into a Microsoft Access database, which had been developed for management of cross-sectional multicenter. The data were analysed using the SPSS version 11.0 (SPSS Inc, Chicago, IL), and the MedCalc® version 10.0 (MedCalc Software, Mariakerke, Belgium).

Results

Demographic and clinical data

The demographic data as well as the RA-specific characteristics of the two cohorts of patients are given in Table I. There was no significant difference in the main demographics characteristics of the subjects of the two cohorts (Group A and B). Their school education level was generally low: 56.1% had received only a primary school education, and only 9.7% had received a high school education. Of the 196 subjects enrolled, 143 (73%) reported 1 or more medical comorbidities, mostly cardiovascular (28.5%), respiratory (13.7%), and metabolic (11.1%) disorders. All patients had active RA,

Table I. Demographic and clinical characteristics of the two cohorts of patients Group A and Group B. Values are mean (standard deviation) unless otherwise indicated.

	Group A (n=196)	Group B (n=247)	*p*
Patients			
Women (%)	83.1	80.1	NS
Age (years)	56.7 (12.1)	58.1 (11.2)	NS
Disease duration (years)	5.1 (5.9)	6.2 (6.6)	NS
Rheumatoid factor positive (%)	78%	76%	NS
Educational level, n (%)			NS
- primary school	110 (56.1)	129 (52.2)	
- secondary school	67 (34.2)	78 (31.6)	
- high school/university	19 (9.7)	40 (16.2)	
No of comorbid conditions, n (%)			NS
- none	53 (27.0)	74 (29.9)	
- 1	50 (25.5)	69 (27.9)	
- 2	46 (23.5)	60 (24.3)	
- 3	21 (10.7)	26 (10.5)	
- 4	11 (5.6)	10 (4.1)	
- 5 or more	15 (7.7)	8 (3.3)	
Swollen joint count (0-28)	8.4 (4.1)	1 (1.1)	<0.0001
Tender joint count (0-28)	12.6 (5.5)	1.5 (3.2)	<0.0001
Self-administered tender joint count (0-10)	4.5 (1.8)	1.5 (1.4)	<0.0001
Patient global assessment of disease activity (0-10)	7.1 (1.7)	2.8 (2.3)	<0.0001
Physician global assessment of disease activity (0-10)	6.8 (1.5)	2.0 (2.2)	<0.0001
Patient global assessment of health status (0-100)	72.9 (16.2)	9.2 (9.8)	<0.0001
Patient assessment of pain (0-10)	7.1 (1.7)	2.5 (2.3)	<0.0001
Health Assessment Questionnaire (0-3)	1.35 (0.58)	0.44 (0.47)	<0.0001
Recent-Onset Arthritis Disability (ROAD) index (0-10)	4.3 (1.9)	1.1 (1.1)	<0.0001
Erythrocyte sedimentation rate (mm/hour)	36.9 (23.7)	15.2 (13.1)	<0.0001
C-reactive protein (mg/dl)	4.9 (2.4)	2.9 (4.8)	<0.001

and the large majority was classified as having moderate or severe disability (41). The proportion of patients in group B achieving MDA or remission were similar: 51% (126 subjects) and 49% (121 subjects), respectively.

Descriptive statistics of composite disease activity indices

Table II summarises the descriptive statistics of all composite disease activity indices. Fig. 2a-b presents estimates of central tendency and distributions for CLARA and PRO-CLARA in the entire patient cohort (Groups A and B). 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). CLARA and PRO-CLARA values were non-normally distributed (Kolmogorov-Smirnov test), as were the other composite indices. CLARA values are considerably shifted to the left compared with PRO-CLARA levels. The means (SD) of PRO-CLARA and of CLARA were 3.36 (2.25) and 2.32 (1.81), respectively. Other overall means (SD) were as follows: DAS28 3.94 (2.03), SDAI 22.81 (18.98), CDAI 19.55 (15.91), MOI-RA 30.68 (23.07), RADAI 3.54 (2.60) and RAPID3 4.02 (2.55) (Table II).

Feasibility

Seventy-two participants (96%) affirmed they had 'no difficulty' in understanding and responding to the items. Two participants found 'some difficulty' and only one respondent seemed to have 'moderate difficulty'. The median time spent completing the self-administered TJC required a median of 1.7 min (range 1.0 – 2.8 minutes), whereas ROAD, and global NRS, were completed by the patients with a median time of 2.1 minutes (range 1.4–2.9 minutes).

Table II. Descriptive statistics of composite disease activity indices.

	PRO-CLARA (range 0-10)	CLARA (range 0-10)	DAS28 (range 0-9.4)	SDAI (range 0-86)	CDAI (range 0-76)	MOI-RA (range 0-100)	RADAI (range 0-10)	RAPID3 (range 0-10)
Lowest value	0.00	0.00	0.00	0.00	0.00	0.14	0.00	0.00
Highest value	8.90	8.70	8.38	75.00	64.00	80.74	9.54	9.66
Arithmetic mean	3.36	2.32	3.94	22.81	19.55	30.68	3.54	4.02
95% CI for the mean	3.15 to 3.57	2.14 to 2.49	3.75 to 4.13	21.04 to 24.59	18.06 to 21.04	28.53 to 32.84	3.30 to 3.79	3.78 to 4.26
Median	3.25	1.8050	3.10	21.01	15.00	24.21	3.11	4.02
95% CI for the median	2.80 to 3.56	1.60 to 2.29	2.95 to 3.65	14.68 to 24.65	11.95 to 22.00	18.51 to 35.52	2.50 to 3.96	3.55 to 4.43
Variance	5.08	3.47	4.14	360.52	253.18	532.66	6.77	6.51
Standard deviation	2.25	1.81	2.03	18.98	15.91	23.07	2.60	2.55
Standard error of the mean	0.10	0.08	0.09	0.90	0.75	1.09	0.12	0.12
Coefficient of Skewness	0.33 (p=0.0041)	0.71 (p<0.0001)	0.37 (p=0.004)	1.59 (p<0.0001)	0.54 (p<0.0001)	0.33 (p=0.0040)	0.29 (p=0.0110)	0.13 (p=0.2437)
Coefficient of Kurtosis	-0.86 (p=0.0042)	-0.31 (p=0.1864)	-1.04 (p=0.001)	8.26 (p<0.0001)	-0.79 (p=0.0072)	-1.27 (p=0.0002)	-1.28 (p=0.0002)	-1.04 (p=0.0012)
Kolmogorov-Smirnov test for Normal distribution	reject Normality (p=0.010)	reject Normality (p<0.001)	reject Normality (p<0.001	reject Normality (p<0.001)	reject Normality (p<0.001)	reject Normality (p<0.001)	reject Normality (p<0.001)	reject Normality (p=0.006)

PRO-CLARA: Patient Reported outcomes (PRO) - CLinical ARthritis Activity; CLARA: CLinical ARthritis Activity; DAS28: Disease Activity Score-28; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; MOI-RA: Mean Overall Index for RA; RADAI: Rheumatoid Arthritis Disease Activity Index; RAPID3: Routine Assessment of Patient Index data 3 (RAPID3).

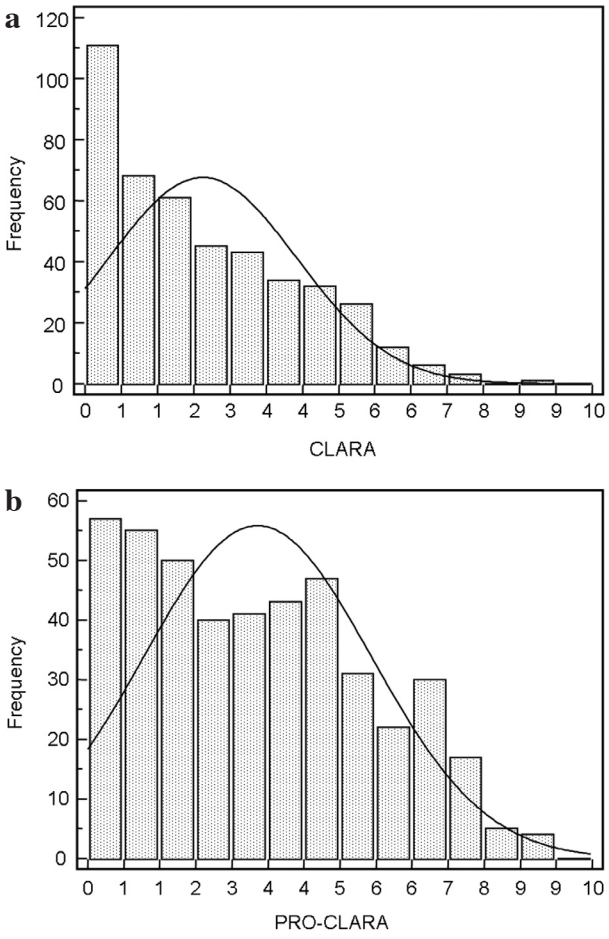

Fig. 2a-b. Overall histogram distribution of CLARA (**a**) and PRO-CLARA (**b**) values in the entire patient cohort (n. 443).

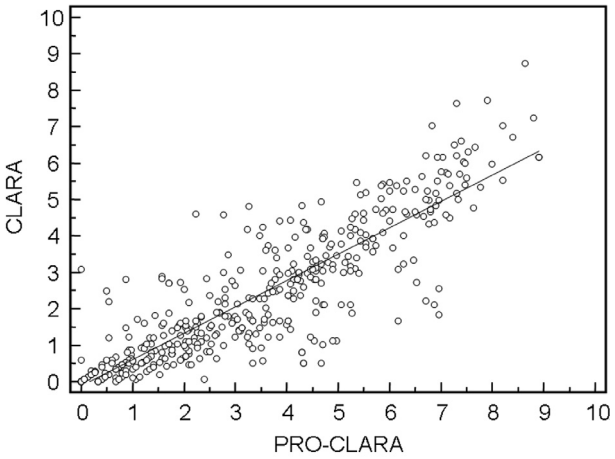

Fig. 3. Scatter plot of CLARA (y-axis) and PRO-CLARA (x-axis) values with a regression line. Each circle shows a single patient's data.

Therefore, PRO-CLARA required a median of 3.8 minutes (range 2.7–4.6 minutes), to complete and about 20 seconds to score. There was a significant age effect, with older patients being slower ($p<0.01$) (data not shown).

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 CLARA and PRO-CLARA were 0.811 and 0.893, respectively, indicating high reliability. Additionally, principal component factor analysis with varimax rotation (Kaiser normalisation) revealed that both the CLARA and PRO-CLARA constitute monocomponent models, explaining 80.6% and 84.2% of the variance, respectively. The higher weighting of self-administered TJC (43.1% of the total variance) than ROAD and the EGA (24.2% and 15.9% of the total variance, respectively) in the PRO-CLARA are of interest. For the CLARA, principal component factor analysis revealed a similar impact of the self-administered TJC upon the total score (43.2% of the total variance), whereas SJC and ROAD exerted a lower influence (20.9% and 16.5% of the total variance, respectively).

Correlational validity

There was a very high degree of correlation between the 2 indices (CLARA and PRO-CLARA) with respect to disease activity (rho=0.880, $p<0.0001$) (Fig. 3). Both indices were also correlated significantly with all other comparator scores (all at a p-level <0.0001) (Table III). The highest correlations were seen between PRO-CLARA and RAPID3 (rho=0.964) and MOI-RA (rho=0.932). The self-administered TJC was correlated with physician's 28-TJC at levels of rho=0.737; $p<0.0001$ (Fig. 4), with SJC (rho=0.726), with HAQ (rho=0.745), with PGA (rho = 0.783), and with EGA (rho=0.733) (all at p-level <0.0001). In addition, CLARA and PRO-CLARA had similar correlations with the HAQ (rho=0.812 and rho=0.840, respectively). On categorising patients into those with no disability, mild, moderate and, severe disability, with respect to the HAQ (41), CLARA and PRO-CLARA were highly significantly different between the four categories (all $p<0.0001$) (Fig. 5) (Kruskal-Wallis test). Significant high correlations ($p<0.0001$) were also seen between CLARA and PRO-CLARA and other self-reported measures, such as ratings of pain (rho=0.822 and rho=0.916, respectively), EGA (rho=0.759 and rho=0.839, respectively), and ESR (rho=0.552 and rho=0.568, respectively). Significant, but less, robust correlations ($p<0.001$) were found with CRP (rho=0.231 and rho=0.178, respectively). The CLARA and PRO-CLARA showed no significant relationship with age, gender, disease duration or number of comorbidities.

Table III. Spearman correlation coefficients for CLARA, PRO-CLARA, and all other indices in the two cohorts of patients (n. 443).

		CLARA	PRO-CLARA	DAS28	SDAI	CDAI	MOI-RA	RAPID3	RADAI
CLARA	Correlation Coefficient		0.880	0.778	0.803	0.812	0.862	0.863	0.827
	Significance level P	---	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
PRO-CLARA	Correlation Coefficient			0.835	0.867	0.897	0.932	0.964	0.902
	Significance level P		---	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
DAS28	Correlation Coefficient				0.872	0.884	0.909	0.838	0.826
	Significance level P			---	0.0000	0.0000	0.0000	0.0000	0.0000
SDAI	Correlation Coefficient					0.962	0.939	0.879	0.863
	Significance level P				---	0.0000	0.0000	0.0000	0.0000
CDAI	Correlation Coefficient						0.931	0.897	0.875
	Significance level P					---	0.0000	0.0000	0.0000
MOI-RA	Correlation Coefficient							0.955	0.912
	Significance level P						---	0.0000	0.0000
RAPID3	Correlation Coefficient								0.903
	Significance level P							---	0.0000
RADAI	Correlation Coefficient								
	Significance level P								---

For abbreviations see Table II.

Discriminant validity

The ROC curves to discriminate the ability of all composite disease activity indices to distinguish patients with active (Group A) and non-active disease (Group B) were similar (Table IV and Fig. 6). From these data, we calculated the cut off values for MDA and remission with the highest combination of sensitivity and specificity. The discriminatory MDA power of CLARA and PRO-CLARA was very good, without significant difference, with an AUC of 0.911 (95% CI 0.874±0.940), and 0.940 (95% CI 0.907±0.963), respectively (differences between areas =0.028±0.013 with 95% C.I. from 0.002 to 0.054; p=0.091) (Fig. 7a). For mACR remission, the discriminatory powers of CLARA and PRO-CLARA were similar, with an AUC of 0.963 (95% CI 0.936±0.981), and 0.959 (95% CI 0.931± 0.978), respectively (differences between areas =0.004±0.008 with 95% C.I. from -0.012 to 0.021; p=0.613), (Fig. 7b). From these data, we obtained the list of sensitivity and specificity for the possible threshold values, and we chose those with the highest diagnostic accuracy (minimal false negative and false positive results) (Table V). The resulting cut off value for CLARA was 2.5 (sensitivity 82.6%; specificity 86.6%) with a LR+ of 6.2, when MDA-OMERACT were used, and 1.5 (sensitivity 86.2%; specificity 93.5%) with a LR+ of 13.3, when the less rigorous *m*ACR remission criteria were used. The cut off point values for the PRO-CLARA were 3.3 (sensitivity 92.3%; specificity 75.4%) with a LR+ of 3.8 and 2.0 (sensitivity 98.3%; specificity 77.0%) (Fig. 7a-b) with a LR+ of 4.4, respectively.

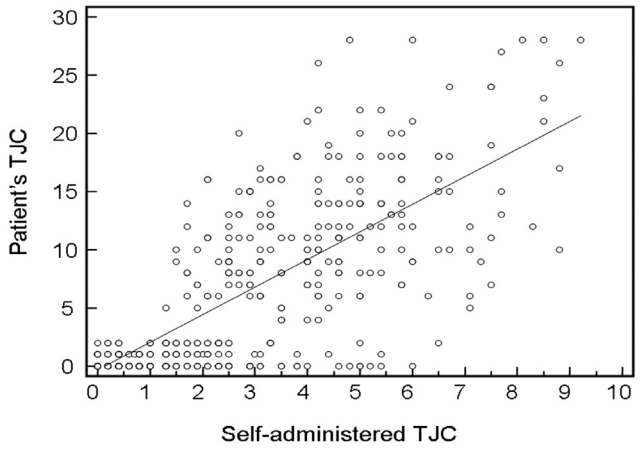

Fig. 4. Scatter plot of patient's tender joint count (TJC) (y-axis) and self-administered TJC (x-axis) values with a regression line. Each circle shows a single patient's data.

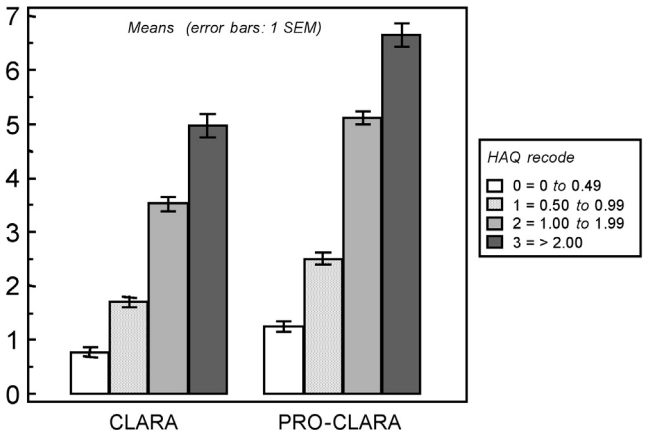

Fig. 5. CLARA scores and physical disability, by Health Assessment Disability (HAQ) index. On categorising patients into those no disability (0 to 0.49), mild (0.50–0.99), moderate (1.00–1.99) and, severe disability (>2.00), with respect to the HAQ, CLARA and PRO-CLARA were highly significantly different between the four categories (all p<0.0001). Bars show mean and SEM of CLARA and PRO-CLARA values

Table IV. AUC-ROC curves values (standard error and 95% confidence intervals) to distinguish patients with active (Group A) and non-active disease (Group B), were similar for all composite indices.

	AUC	SE	95% CI
PRO-CLARA	0.949	0.011	0.924 to 0.968
CLARA	0.938	0.012	0.911 to 0.958
DAS28	0.944	0.012	0.919 to 0.964
SDAI	0.956	0.010	0.932 to 0.973
CDAI	0.959	0.010	0.936 to 0.976
MOI-RA	0.952	0.009	0.930 to 0.971
RADAI	0.947	0.011	0.922 to 0.966
RAPID3	0.939	0.012	0.912 to 0.959

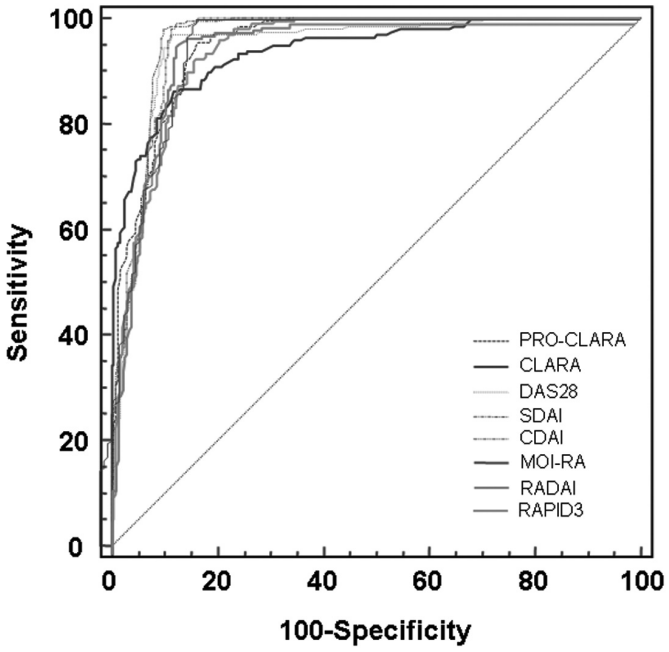

Fig. 6. Receiver operating characteristic (ROC) curves for the performance of composite disease activity indices in discriminating between patients with active (Group A) and non-active disease (Group B). The closer the curve approaches the upper-left corner of the graph, the more informative the instrument is.

Discussion

With the increasing availability of biological therapies for patients with RA, the need to monitoring disease activity by composite indices, a combination of surrogates related directly to the inflammatory events, such as joint counts and the acute-phase response, is regarded as obligatory (18, 21). A numerical measure of disease activity, as provided by the DAS28 and the EULARC, as well as the SDAI and CDAI, gives the opportunity of comparing the disease status of patient groups or of individual patients (58). These indices are also widely recommended for disease activity monitoring in clinical practice. Achieving low disease activity, at best a remission-like state, is regarded as essential in improving prognosis (59, 60). Nevertheless, only a small percentage of rheumatologists have incorporated these tools into their standard, everyday clinical practice (21, 26, 61). Cush *et al*. reported that only 12% of rheumatology collect and score HAQ and only 6% calculate DAS as part of their routine clinic visit (62). This is likely due to the time required to administer a questionnaire, assess the patient's joint pain and swelling, score the results, and record the information in a readily retrievable format. In addition, all indices to assess disease activity in RA have some shortcomings. DAS includes 4 variables, and it requires complex calculations like square root and logarithm. Further, DAS, SDAI, and CDAI require a formal quantitative joint count and do not include patient functional status (HAQ). The ACR20/50/70 response criteria, as well as ACR hybrid (5), are based on change in disease activity and do not allow assessment of the current disease activity; therefore, they cannot be used in cross-sectional settings. Regarding RA outcome assessment, there is currently a trend to develop PRO measures (63). The domains of highest importance of these PROs are pain, functional disability, fatigue, emotional and physical well-being, sleep disturbance and coping (63). The validity and usefulness of PRO data in evaluating and monitoring patients with RA have been well documented (64-67). PROs have been found to be informative and are an attractive option in a busy medical practice, as the time burden is transferred from the clinician to the patient. Instruments for measuring PROs that are easier to administer and less expensive than physician-observed disease activity and process measures, exhibit reliable information about disease activity, and provide an alert in case of deterioration could improve and standardise daily routine care significantly. These data have traditionally been collected on paper, but more trials are using electronic means to capture PRO (ePRO). The use of computer touch-screen technology for the collection of the PRO data in the rheumatologic setting is an acceptable, and in many cases, a preferable option to paper (68). This favourable reaction is consistent with other studies that have used touch-screen technology to collect PRO information (69-71). In our touch-screen computerised format the questions have been shown in a cartoon, written and spoken. The patients can answer by touching the screen directly. This interface is a particular attractive one, as it could easily be used by a wider range of patients than keyboard or mouse options. The experience indicates that this may be important if non-computer skilled persons or senior citizens are using the computerised version of the PRO-CLARA. The quality of the numerical PRO data collected with this electronic touch-screen version was excellent, with no missing or problematic responses (68). Electronic data collection improves data quality by providing software safeguard against entry omission and inconsistent

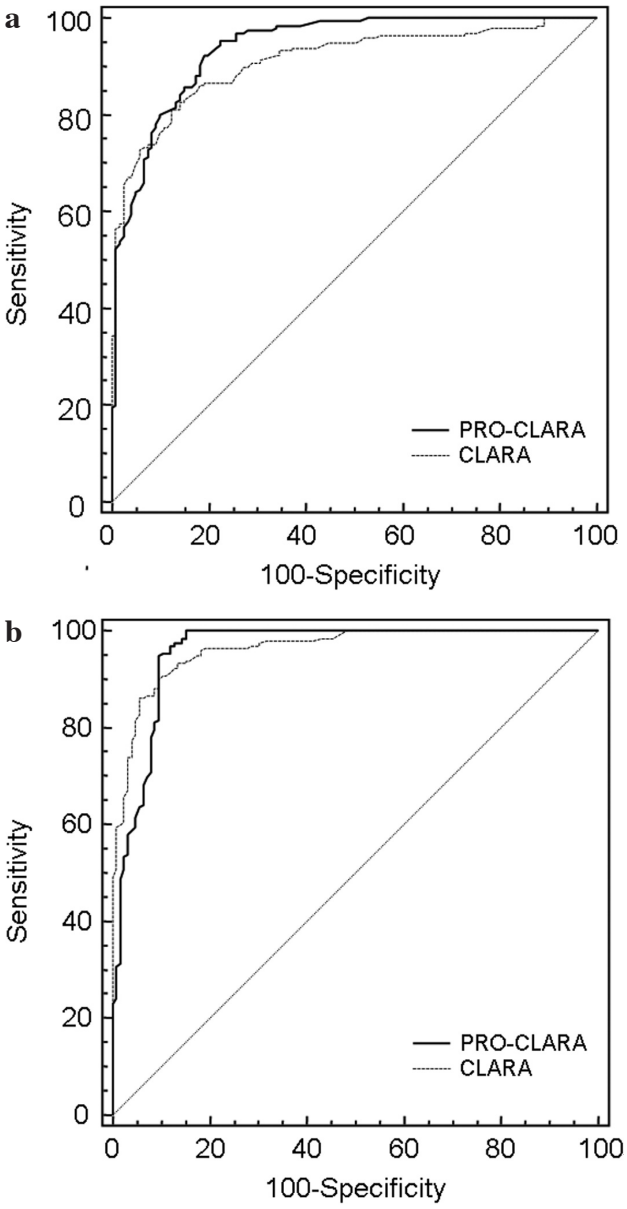

Fig. 7. Receiver operating characteristic (ROC) curves of the CLARA and PRO-CLARA when used to discriminate the minimal disease activity (MDA) or remission using the OMERACT definition of MDA (**a**), or the ACR modified criteria for remission (mACR) (**b**). The curves plot the relationship between the sensitivity and 1–specificity of CLARA and self-CLARA for different cut off levels of test positivity.

response sets, and by completely eliminating data entry errors at the researcher's level.

Previous studies on the psychometric properties of composite indices based purely on PROs, such as the Patient Activity Scale (PAS), the RADAI or the RAPID3 index, have demonstrated adequate reliability, validity and responsiveness of these indices among patients with RA and proven them to be feasible, informative quantitative measures for busy clinical settings (29-31, 34, 72). Data from patients concerning RAPID3 score which does not require a formal joint count appear adequate to document status and monitor effectiveness of therapies in RA patients, and are substantially more easily obtained than DAS, SDAI or CDAI (33).

These considerations have led us to develop an index, termed PRO-CLARA, and to analyse its validity and measurement properties in two different clinical settings in order to facilitate rapid and easy RA activity assessment in daily routine. The PRO-CLARA, excluding physician's joint count, combines the 3 self-report RRO measures – patient assessment of tender joint, functional disability and patient global assessment - in a simple numerical summation that required a median of 3.8 minutes to complete and which can be scored in about 20 seconds. A receptionist, nurse clinician, or other assistant can be taught easily to calculate PRO-CLARA score using the scoring templates (Fig. 1) as used by the authors in this study. The introduction of computer touch-screen technology into our clinic resulted in 100% compliance with completion of all the items of the questionnaire (68).

The content validity of the PRO-CLARA is based on the fact that these assessed measures are included in the highly validated measures of disease activity (24, 73), in the EULARC and in the OMERACT/ILAR/WHO (International League Against Rheumatism/ World Health Organisation) guidelines (38).

The joint count is the most specific measure for RA, and a careful examination of joints is required to formulate clinical management decisions; a patient questionnaire certainly is not regarded as a substitute for a joint examination. Nonetheless, important limitations are overlooked in the rheumatology literature (35), including poor reliability (74, 75), lesser sensitivity to detect inflammation than musculoskeletal ultrasound (76), and lesser prognostic value than physical function scores for important severe long term outcomes (35). As Pincus *et al*. point out "a formal quantitative joint count which is not performed by most rheumatologists at most visits may not be necessary to monitor patients quantitatively in a busy, clinical care setting" (21). The self-administered TJC exhibited adequate reliability and construct validity in patient with RA (77). Therefore, a qualitative joint count supplemented by a self-administered TJC, rated in a joint list, may be adequate for most patient care and preferable to no quantitative data at all, which is usually the case in usual clinical setting. Our previous results have demonstrated that touch-screen administration of the joint assessment questionnaire would be acceptable to the majority of patients with a high level of agreement with the paper format (68). The validity of the patient-reported TJC on touch-screen was also supported by the significant correlation with other self-reported measures such as ratings of pain, physical disability and disease activity.

Table V. The estimated cut-off points of CLARA and PRO-CLARA corresponding to the MDA-OMERACT and the mACR remission criteria.

	CLARA		PRO-CLARA	
	MDA-OMERACT (95% CI)	mACR remission (95% CI)	MDA-OMERACT (95% CI)	mACR remission (95% CI)
Cut-off point	2.5	1.5	3.3	2.0
Area under ROC curves	0.911 (0.874 to 0.940)	0.963 (0.936 to 0.981)	0.940 (0.907 to 0.963)	0.959 (0.931 to 0.978)
Sensitivity (%)	82.6 (78.5 to 87.6)	86.2 (80.5 to 90.7)	92.3 (87.6 to 95.6)	98.3 (96.5 to 99.9)
Specificity (%)	86.6 (79.6 to 91.8)	93.5 (88.1 to 97.0)	75.4 (67.2 to 82.4)	77.0 (69.1 to 83.7)
LR+	6.2	13.3	3.8	4.4

MDA-OMERACT: Minimal Disease Activity - Outcome Measures in Rheumatology Clinical Trials; mACR: modified American College of Rheumatology remission criteria; ROC: Receiver operating characteristic; LR+: likelihood ratio positive (ratio of the sensitivity of a test to the false positive error rate of the test).

Physical disability is the most powerful determinant of all severe long-term outcomes in RA, such as work disability (78), mortality (27), costs (79), the need for joint replacement surgery (80), and loss of function (81). Data from self-report patient questionnaires are recognised as valid and reliable (82). Questionnaires are valuable research tools but generally are not incorporated into routine medical care, mainly because of their length, extra time needed to administer and complete the questionnaires, and complex and non-intuitive scoring systems. The ROAD is a valid, reliable, and responsive instrument for a brief, simple assessment of functional disability in RA patients (43,44). It is easily completed by patients and scored by health professionals in standard clinical care.

The inclusion in PRO-CLARA of patient's global assessment, as a parameter of clinical evaluation of disease activity in RA, could be viewed as redundancy or duplication. However, there are substantial data indicating that the patient's global assessment was the patient measure that correlated most highly with the most accurate physician-determined measure and with the physician assessment of disease activity (83). Moreover, the patient's perception of health determines the ability of the patient to cope with disease as well as to comply with treatment.

Our results extend previous observations that indices of only PROs measures showed satisfactory psychometric properties in patients with RA (29-31, 34, 72). The PRO-CLARA performed identically to other composite tools, such as the DAS28, SDAI, CDAI and MOI-RA and with those including only PRO measures, such as RAPID3 and RADAI. Omission of the 28-SJC in the PRO-CLARA did not harm the psychometric qualities of the index. Feasibility and acceptability to patients can be regarded an important requirement of any assessment measure. In terms of feasibility, a vast majority of patients (96%) can complete the PRO-CLARA. In addition, there was a low rate of items that were not filled in at all, so the acceptance seems to be good. Internal consistency testing of both CLARA scores indicated a reasonable difference, with Cronbach's alpha slightly higher for the PRO-CLARA. Additionally, results of the principal component factor analysis revealed that both CLARA indices constitute monocomponent measures in RA. Interestingly, factor analysis showed that the self-administered TJC was found to exert the highest influence upon the total score for both CLARA indices. Furthermore, the TJC performed by a physician or Ritchie index has a major effect on the DAS and CDAI scores that could lead to overestimation of disease activity in individual patients due to the component TJC (18, 84, 85).

The construct validity was demonstrated by correlating CLARA scores with all other composite indices. The correlation among scores obtained using the different disease activity status measures is very good, with the smallest rho correlation coefficient being 0.778. These data are similar to previously published data (86, 87). The self-administered TJC is correlated with a TJC by a physician at levels of $p<0.0001$. The strong association of self-administered TJC and SJC, PGA, EGA, and physical disability, highlight that pain is an important measure when the patient perspective on outcome assessment is taken into account (65, 67).

We further explored the ability of the CLARA indices to discriminate between disease activity levels using ROC analysis. The AUC of the PRO-CLARA, excluding physician's joint count, gives identical results to those provided by CLARA or other composite indices. This is illustrated by comparing the AUCs in Fig. 5. PRO-CLARA 3.3 and 2.1 cutoff points correspond to fulfilment of the MDA-OMERACT and less rigorous *m*ARA remission criteria, respectively.

Limitations to this study are seen in addition to specific limitations of each analytic method. A primary limitation which must be emphasised is that repeatability of PRO-CLARA was not studied. However, repeatability of the 3 components of PRO-CLARA has been studied on several occasions, since they all are components of ACR Core Set criteria and widely accepted in RA assessment. A further limitation concerns the generalisability of the results. For this investigation we used two different cohorts of patients with RA. The first cohort comprised active RA patient who were treated with DMARD therapy and are planning to start a TNF-α antagonist treatment. The second source of data was a cohort of patients with RA

participating in a long-term observational study who satisfy MDA and remission definition criteria while taking conventional DMARDs or biologic agents. Therefore, the results should be generalised with caution to the whole population of patients with RA and other treatments.

Based on these different clinimetric properties within the present study, we conclude that the PRO-CLARA is feasible in its use by patients and can validly assess disease activity in RA out-patients. Compared to the CLARA version (omitting joint count), the PRO-CLARA proved to be highly reliable and valid. The computer touch-screen PRO-CLARA version could improve the quality of data collection in clinical trials by computer-based direct data collected and contribute to more active participation of the patients. In addition, it could simplify its use both in the research setting and in daily clinical practice. Of course, further validation of the index will be required to fully confirm its value in other patient populations. Such additional investigations should include analyses of construct validity with regard to radiographic damage and prognostic values of cut off points in MDA and remission. Such analyses are currently underway.

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