

The comparative responsiveness of the patient self-report questionnaires and composite disease indices for assessing rheumatoid arthritis activity in routine care

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Abstract

Objectives

This paper aims to evaluate the internal and external responsiveness of the patient self-report questionnaires, comparatively to the traditional composite indices to assess the activity of rheumatoid arthritis (RA) in everyday practice.

Methods

One hundred and ninety-one RA out-patients completed the clinical arthritis activity (PRO-CLARA) index, the rheumatoid arthritis disease activity index (RADAI), the routine assessment of patient index data (RAPID3), and the patient activity score (PAS). Simultaneously, the disease activity score-28 joints based on CRP (DAS28-CRP) and ESR (DAS28-ESR), the simplified disease activity index (SDAI), the clinical disease activity index (CDAI), and the mean overall index for RA (MOI-RA) were computed for each patient. Sensitivity to change was assessed after 6 months of treatment with disease-modifying anti-rheumatic drugs or biologics. Internal responsiveness was evaluated with the effect size (ES) and standardised response mean (SRM). External responsiveness was investigated by receiver operating characteristic (ROC), in categories of respondents, stratified according to the response on an item on change in overall health. In addition, change scores were compared by calculating correlation coefficients.

Results

No significant differences in internal and external responsiveness were found between self-report questionnaires and composite indices. The internal responsiveness of the self-report questionnaires and composite measures was wide, with SRM and ES ranging from 1.03 (RADAI) to 1.80 (DAS28-ESR) and higher than that of the each individual measures. The responsiveness of the PRO-CLARA was equal to the DAS28-ESR, DAS28-CRP, SDAI or MOI-RA, but better than the CDAI. The RADAI and PAS were less responsive than the PRO-CLARA and RAPID3. The area under ROC curve of the PRO-CLARA gives identical results to those provided by other comparator composite indices. The score changes of all combinations were highly correlated ($p < 0.0001$).

Conclusion

The self-report questionnaires showed comparable internal and external responsiveness to the composite activity scores and allow for the detection of rheumatoid disease activity. They appear suitable for clinical decision making, epidemiologic research and clinical trials. Further longitudinal studies are needed to validate these encouraging results.

Key words

rheumatoid arthritis, composite indices, patient self-report questionnaires, disease activity, responsiveness

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Received on December 22, 2011; accepted
in revised form on March 21, 2012.

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Introduction

Traditional composite measure of disease activity in rheumatoid arthritis (RA), such as the Disease Activity Score, based on erythrocyte sedimentation rate (DAS28-ESR) (1, 2) or C-reactive protein (DAS28-CRP) (3, 4), simple Disease Activity Index (SDAI) (5), Clinical Disease Activity Index (CDAI) (6) or the Mean Overall Index for Rheumatoid Arthritis (MOI-RA) (7) and their respective cut-off levels for low disease activity (LDA) and remission (no activity), are tools that can be used in routine care in patients with undifferentiated arthritis and in established RA patients. All these indices include a formal joint count of tender and swollen joints performed by a physician/assessor. The joint count is the most specific measure to assess RA activity and it is regarded by rheumatologists as the most important assessment measure (8). However, most visits of patients with RA performed by rheumatologists do not include a formal quantitative joint count (9), and patient care generally is guided only by a careful, but no quantitative, history and physical or ultrasonographic examination (9, 10). Additionally, it is well established that joint counts are time consuming and depend on the interobserver variation (11). Each of the 7 RA core data set measures has similar relative efficiencies to distinguish active from control treatments in clinical trials (12, 13). Therefore, indices composed of only the 3 patient-reported core data set measures (physical function, pain, patient global estimate) without joint counts are reliable as the whole core set used to assess RA activity changes (14).

More recently, self-report questionnaires have become increasingly important for the evaluation of RA (5, 15). They are easier to complete, non invasive, with no additional costs and they showed good psychometric properties (15-18). Previously, we analysed the performance of a new self-report questionnaire to assess rheumatoid arthritis activity, termed PRO-CLARA (PRO-CLinical ARthritis Activity) (19), combining a patient's physical function (20-22), self-administered tender joint count (TJC) and patient's global assess-

ment into a single measure of disease activity, in a cross-sectional study of patients with RA. Self-administered PRO-CLARA, similarly to the the "Routine Assessment of Patient Index Data 3" (RAPID3) (23) and to the Patient Assessment Score (PAS) (24), has primarily been developed for use in clinical and epidemiological studies where clinical assessments are not available or too demanding. The Rheumatoid Arthritis Disease Activity Index (RADAI), developed for use in epidemiological studies, combines a patient's perception of past disease activity, current disease activity as measured by swollen and tender joints, pain, duration of morning stiffness and tender joint count (25). All the above mentioned patient self-administered tools have shown to be capable to measure RA activity accurately in comparison with DAS28, SDAI and CDAI indices (23, 26). Further information regarding their responsiveness or sensitivity to change would add the evidence that these indices might be useful to assess RA patients in routine clinical care. Responsiveness is an important clinimetric parameter for measurement instruments that aim to measure change over time, for example, outcome measures in studies on the effects of treatment (27, 28). Although the most appropriate responsiveness statistic remains a matter of debate, the important distinction between responsiveness measures that quantify the treatment effect (effect size or standardised response mean) and measures that focus on the longitudinal construct validity by assessing the correlation of change scores with another measure (external standard) for change (29-31), has to be highlighted. The aim of the present study was to compare the internal and external responsiveness of various traditional composite disease activity indices and self-report questionnaires in an observational cohort of patients with RA, treated with disease-modifying anti-rheumatic drugs (DMARDs) or biologic agents.

Patients and methods

Patients

One hundred and ninety-one patients with RA consented to participate in a multicentre prospective study of RA

Funding: This study was supported by Wyeth (acquired by the Pfizer Group), without having influenced the manuscript content.

Competing interests: none declared.

cohort, termed the NEW INDICES study (19, 22). Clinical details of these patients were previously described (19). All patients were on DMARDs (≥ 1) or on a combination of methotrexate plus anti-TNF agent treatment and were sequentially evaluated for at least six months. The patient selection criteria were the fulfilment of the ACR 1987 revised criteria for RA (32), age 18–75 years, and active disease, with at least 3 of the following 4 features: either ESR ≥ 28 mm/hour or a CRP level > 19 mg/dl, morning stiffness ≥ 30 minutes, ≥ 5 swollen joints, and ≥ 10 tender joints (33). The involved rheumatologists were instructed to collect the data following standard definitions and procedures. The patients represent a “real life” sample of population with RA that can be seen at each centre. Ongoing, instituted and withdrawn medication with DMARDs, biological agents, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and analgesics was registered at all visits. Drug treatment decisions were made by the physician's preference. The protocol was approved by the national health authorities and ethics committees in all participating hospitals. All the patients gave informed written consent.

Traditional composite diseases indices and PRO questionnaires

Clinical assessments comprised the following single measures of disease activity: 28 joint counts for swollen and tender joints (SJC and TJC, respectively), patient self-administered TJC (as described below), pain numerical rating scale (NRS-pain, 0–10), evaluator and patient assessments of disease activity (EGA, PGA, respectively) measured with a numerical rating scale (NRS 0–10), patient's general health status (PtGH) by NRS (0–100). Laboratory tests were the following: erythrocyte sedimentation rate (ESR, Westergren method) and C-reactive protein (CRP, Elisa). In addition, all patients completed the Health Assessment Questionnaire Disability Index (HAQ-DI) (34), and the Recent-Onset Arthritis Disability (ROAD) questionnaire (20, 21). The HAQ-DI assesses the degree of difficulty a person has in accomplish-

ing tasks in 8 functional areas: dressing and grooming, arising, eating, walking, hygiene, reach and grip activities. For each item, patients were asked to rate the level of difficulty over the past week on a 4-point scale, which ranges from 0 (no difficulty) to 3 (unable to perform). The disability score ranges from 0 to 3, with a higher score indicating more severe disability. The HAQ-DI, calculated for each of the subscales, is summed and then divided by 8. An adapted version of HAQ-DI for use among Italian patients was used in the present study (35). 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, activities of the lower extremity, and activities that involve both upper and lower extremities (20). For each item patients are asked to rate the 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 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 the best status and 10 representing the poorest status (20). These variables were used to calculate both the traditional composite disease activity indices, such as the DAS28-ESR (1, 2), the DAS28-CRP (3, 4), the SDAI (5), the CDAI (6), and the MOI-RA (7), and the patient self-report questionnaires, such as the RADAI (25), the PRO-CLARA (19), the RAPID3 (23), and the PAS (24) (as described below).

Composite diseases activity indices

The DAS28-ESR includes 28-SJC and 28-TJC in addition to PtGH and ESR values (1, 2). The DAS28 based on CRP concentration (DAS28-CRP) combines information from the 28 tender and swollen joints, the CRP (in mg/dl) and the PtGH (3, 4). Both DAS28-ESR and DAS28-CRP were calculated by a website calculator (DAS Score NL: disease activity score in rheumatoid arthritis; available at: <http://www.das-score.nl/www.das-score.nl/index.html>).

The DAS28 ranges 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 ($3.2 < \text{DAS28} \leq 5.1$), or as high disease activity (DAS28 > 5.1) (42, 44). A DAS28 < 2.6 corresponds to remission (36). The SDAI (5) and the CDAI (6) have been developed to provide physicians and patients with simple and more comprehensible instruments. The SDAI employs a linear sum of five untransformed, unweighted variables, including 28-SJC and 28-TJC, PGA EGA on an 11-point NRS, and CRP (5). 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 (5, 37, 38). The CDAI is a modification of the SDAI without laboratory evaluation (CRP) to allow for immediate clinical assessment (6). The CDAI score is computed as follow: CDAI = SJC + TJC + PGA (in cm) + EGA (in cm). The range of CDAI is 0–76. Thresholds to separate remission, low and moderate levels of disease activity are at 2.8, 10 and 22, respectively (37, 38). 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) (7). 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 indicating poorer outcomes (7).

Patient self-report questionnaires

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) (25). The last two items are scored on a 7-point and 4-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 it ranges from 0 to 10 (25, 39). 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, self-administered TJC and PGA into a single measure of disease activity [19]). The self-administered TJC was evaluated according to joint list of the RADAI. 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 (25). The self-administered TJC weighted the degree of tenderness of each joint on the following scale: 0=none, 1=mild, 2=moderate, 3=severe (10) (25). The self-administered TJC is scored as 0–48; the raw 0–48 score may be recoded to 0–10 using a scoring template. The PGA, is scored 0–10 on an 11-point NRS, with the following 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 it ranges from 0 to 10. The routine assessment of patient index data 3 (RAPID3) is an index of only the three PRO measures – physical function, pain and global status – that appear adequate to document status and monitor effectiveness of therapies in patients with RA (23), and are substantially more easily obtained than DAS, SDAI or CDAI in standard clinical care (40). To calculate RAPID3, the raw 0–3 score for physical function on the modified HAQ (MHAQ) is converted to 0–10 using a scoring template (40). Pain and global estimate are assessed according to 11-point NRS, both scoring 0–10. The three 0–10 scores for physical function, pain NRS and global NRS, are added together for a raw score of 0–30,

and divided by 3 to give an adjusted 0–10 score. Proposed severity (rather than activity) categories for RAPID3 are the following: >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 follows: >12 =high, 6.01 – 12 =moderate, 3.01 – 6 =lower, and ≤ 3 =near-remission (41). The PAS contains three items on physical disability, pain and global health. We formed the PAS by multiplying the HAQ by 3.33 and then dividing the sum of the VAS pain, VAS global, and HAQ by 3. This yields a 0–10 scale (24).

Statistical analysis

Continuous data were presented as means with standard deviations (SDs) (tested with the Kolmogorov-Smirnov test). Categorical data were presented as proportions. Responsiveness was evaluated by longitudinal assessment of patients, investigating if the measures were sensitive to change following the intervention. Responsiveness refers to the ability of an elicitation method to accurately detect a meaningful change in belief over time when it has occurred (27–30). In accordance with Husted *et al.*, we distinguished between internal and external responsiveness (42). To assess the magnitude of the internal responsiveness, we calculated the effect size (ES) and standardised response mean (SRM) (27, 28, 31). The ES is defined as the mean change in the score between baseline and follow-up, and this mean change is divided by the SD of the baseline score. The SRM is defined as the mean change in the scores between baseline and follow-up, and this change is divided by the standard deviation (SD) of the individual changes in the scores (27, 28). The higher the SRM or ES, the greater the responsiveness. Values ≤ 0.5 , between 0.5 and 0.8, and ≥ 0.8 were considered to represent small, moderate and large degrees of responsiveness, respectively (27, 28, 31). Calculation of 95% CI was performed by bootstrap. Since each of these indices looks at change for the declined group, we supplemented them by computing the paired *t*-test statistic for the difference in change scores. Change be-

tween baseline and 6-month follow-up assessments was considered significant when $p < 0.05$. External responsiveness was investigated with receiver operating characteristic (ROC) curve analysis in categories of respondents, stratified according to the response on an item on change in overall health during the previous 6 months. We used the second item of the SF-36 questionnaire as transitional questionnaire and as a criteria to dichotomise improved patients (much better, somewhat better) and those not improved (about the same, somewhat worse, much worse). This item was modified from the original version of SF-36 questionnaire according to the purpose of the study as follows: “compared to 6 months ago, how would you rate your health in general now? (1=much better, 2=somewhat better, 3=about the same, 4=somewhat worse, 5=much worse)”. This method has the advantage of synthesising information on the sensitivity and specificity for detecting improvement by an external criterion (31). The area under the ROC curve (AUC-ROC) in this setting can be interpreted as the probability of correctly identifying the improved patients from non-improved patients. The area ranges from 0.5 (no accuracy in distinguishing improved from non-improved) to 1.0 (perfect accuracy) (43). According to Swets (43), areas 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. Since ROC analysis requires external criteria to be dichotomous, the categories of “about the same, somewhat worse” and “much worse” were collapsed to one variable (non-improved patients) for our analysis. To further investigate the external responsiveness, change scores among the patient self-reported questionnaires and the composite indices were compared by calculating correlation coefficients (Pearson’s correlation coefficient). All data were entered into a Microsoft Access database, which had been developed for management of cross-sectional multicentre. The data were analysed using the MedCalc® version 11.0 (MedCalc Software, Mariakerke, Belgium) and the SPSS software (version 11.0) for Windows XP.

Results

Demographic and clinical data

The RA cohort is made up of 191 patients (158 women and 33 men); the mean age was 56.6 ± 12.2 years and the mean duration of disease was 5.1 ± 5.5 years. Their school education level was generally low: 56.2% had received only a primary school education, and only 9.8% had received a high school education. Of the 191 subjects enrolled, 140 (73.3%) reported one or more medical comorbidities, mostly cardiovascular (28.9%), respiratory (13.2%), and metabolic (11.8%) disorders. All patients had active RA and the large majority was classified as having moderate or severe disability (26). At baseline, 171 patients (89.5%) received DMARDs or biologic therapy, 104 patients (54.4%) received methotrexate monotherapy, 34 patients (17.8%) received antimalarials, 20 patients (10.5%) received leflunomide, 13 patients (6.8%) received sulfasalazine, 4 patients (2.1%) received cyclosporine A and 15 patients (8.1%) received a combination of tumour necrosis factor (TNF) blockers including infliximab, etanercept and adalimumab or anakinra and methotrexate. A total of 98 patients (51.3%) underwent corti-

costeroids (mean 3.9 mg prednisolone/day) therapy and all patients received non-steroidal antirheumatic drugs, at least on demand. During the study, 184 patients (96.3%) received conventional DMARDs or biologic agents: 47.8% received methotrexate monotherapy, 23.9% received a combination of methotrexate and DMARDs (antimalarials and sulfasalazine) and 28.3% received a combination of methotrexate and anti-TNF blockers.

Score distributions of the patient self-report questionnaires and composite indices

Figures 1 and 2 show estimates of central tendency and distribution of score for self-report questionnaires (Fig. 2) and traditional composite disease activity indices (Fig. 1) of RA patients at baseline. 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). All self-report questionnaires and composite indices were normally distributed (Kolmogorov-Smirnov test). Therefore, the parametric analyses were used.

Internal responsiveness effect size and standardised response mean statistics

The self-report questionnaires were responsive measures with ES and SRM values similar to the traditional composite indices (Table I). The most efficient composite measures in detecting changes were the DAS28-ESR, (ES=1.80 and SRM=1.35) and the DAS28-CRP (ES=1.74 and SRM=1.46). The composite measure least responsive in detecting change was the CDAI (ES=1.50 and SRM=1.24). The responsiveness of PRO-CLARA (ES=1.75 and SRM=1.42) was similar to the DAS-28 ESR and the DAS-CRP and to the SDAI and MOI-RA, but slightly higher than RAPID3 (ES=1.64 and SRM=1.26). The least responsive self-report questionnaire was the RADAI with an ES of 1.36 and an SRM of 1.03 (Table I).

External responsiveness receiver operating characteristic (ROC) curve analysis

Figure 3a shows the ROC plots of changing scores of the five traditional composite disease activity indices (DAS28-ESR, DAS28-CRP, SDAI,

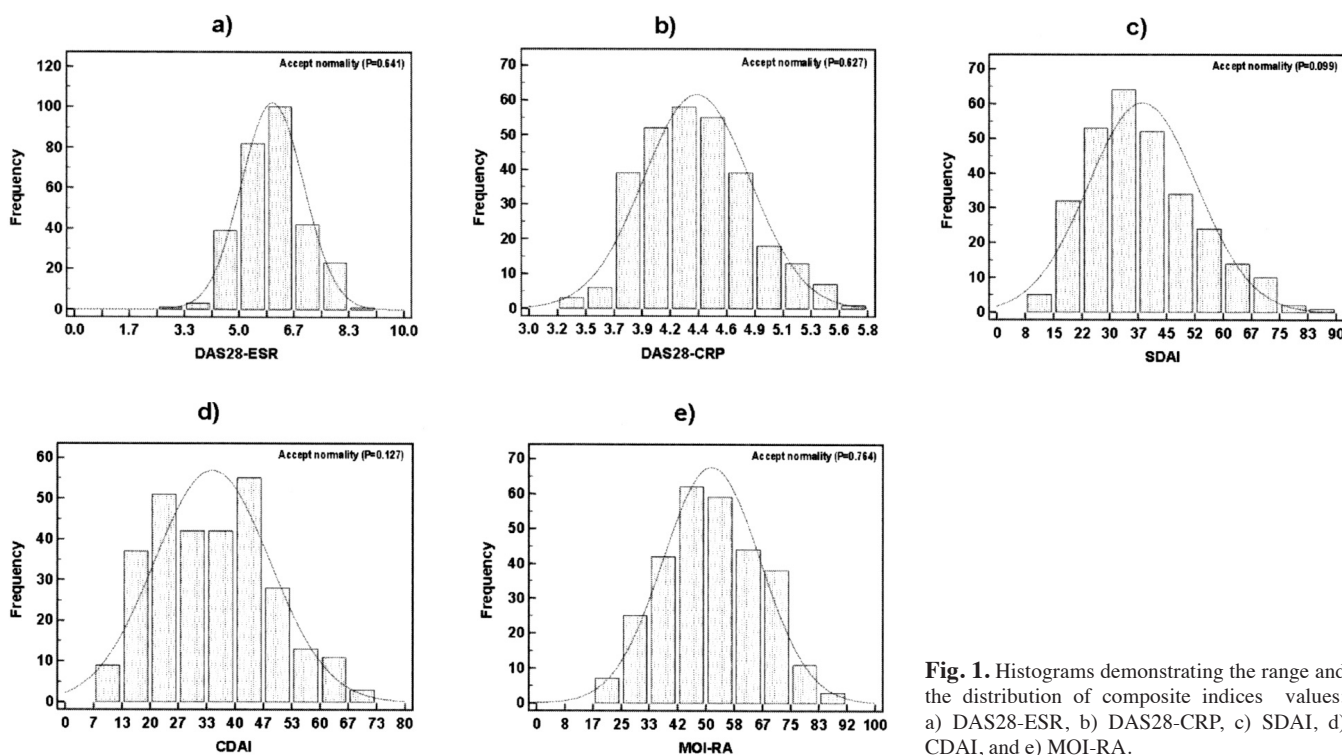


Fig. 1. Histograms demonstrating the range and the distribution of composite indices values: a) DAS28-ESR, b) DAS28-CRP, c) SDAI, d) CDAI, and e) MOI-RA.

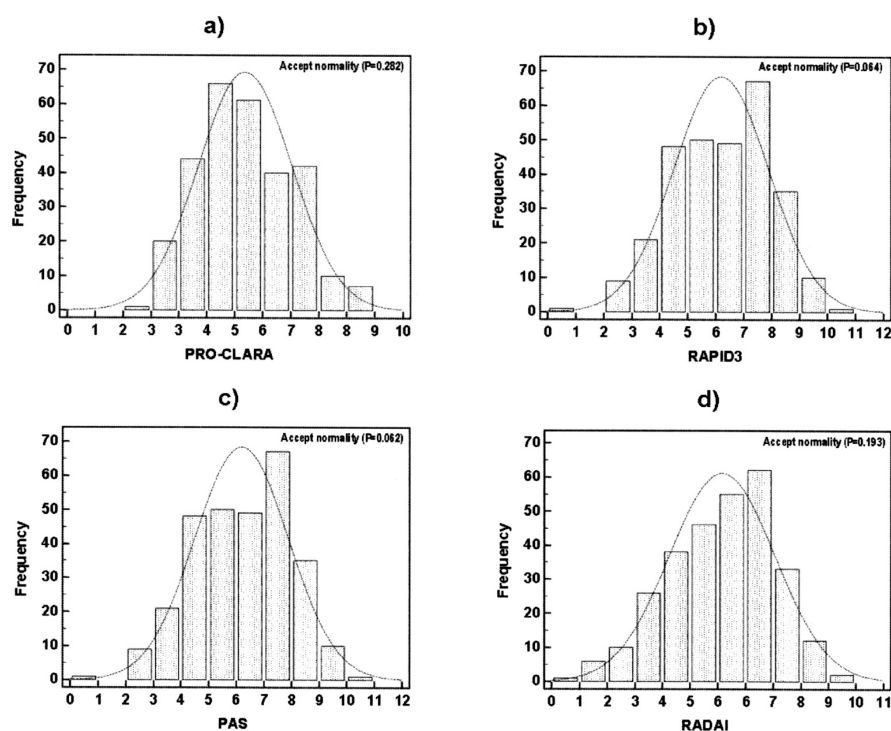


Fig. 2. Histograms demonstrating the range and the distribution of PRO questionnaires values: a) PRO-CLARA, b) RAPID 3, c) PAS, and d) RADAI.

CDAI and MOI-RA). Figure 3b shows the four self-report questionnaires (PRO-CLARA, RAPID3, PAS and RADAI). The area under ROC curve (AUC) was used to evaluate the screening method's performance. At the end of follow-up, according to the transitional questionnaire, the result was that 143 patients improved, while 48 patients did not improve or change. Regarding DAS28-ESR and DAS28-CRP, the AUC were 0.837 ± 0.023 (95% CI

$0.790\text{--}0.878$) and 0.826 ± 0.023 (95% CI $0.778\text{--}0.868$), respectively. With regard to the SDAI and CDAI, the AUC were 0.827 ± 0.024 (95% CI $0.778\text{--}0.868$), and 0.825 ± 0.023 (95% CI $0.777\text{--}0.867$), respectively. Regarding MOI-RA, the AUC was 0.839 ± 0.023 (95% CI $0.792\text{--}0.880$). Concerning the ROC plots of the change score of self-report questionnaire, the AUC related to PRO-CLARA and RAPID3 were 0.823 ± 0.024 (95% CI 0.774--

0.865), and 0.801 ± 0.025 (95% CI $0.750\text{--}0.845$), respectively, whereas the AUC of the PAS and RADAI were 0.785 ± 0.026 (95% CI $0.733\text{--}0.831$) and 0.773 ± 0.027 (95% CI $0.721\text{--}0.821$), respectively. The difference between changing scores of PRO-CLARA and RADAI is significant (differences between areas $= 0.050 \pm 0.026$ with 95% CI $0.001\text{--}0.101$; $p = 0.048$).

Comparison of score changes by longitudinal analysis

To further investigate the external responsiveness, change scores among the patient self-reported questionnaires and the composite indices were compared by calculating correlation coefficients. The score changes of all combinations were highly correlated ($p < 0.0001$) (Table II). In particular, there was a strong correlation between mean change of the PRO-CLARA and RAPID3 scores ($r = 0.818$, $p < 0.0001$) and between RAPID3 and PAS scores ($r = 0.891$, $p < 0.0001$). Changes in the PRO-CLARA score was also significantly correlated with changes in the PAS ($r = 0.712$, $p < 0.0001$) and in the RADAI ($r = 0.701$, $p < 0.0001$). Similarly, we have found a strong correlation between mean change in the DAS28-ESR score with changes in the DAS28-CRP ($r = 0.787$, $p < 0.0001$) and between mean change in the SDAI and CDAI score ($r = 0.945$, $p < 0.0001$). Given that DAS28-CRP is derived from DAS28-ESR and that CDAI is derived from

Table I. Internal responsiveness of the composite disease activity indices and the patient-self reported questionnaires.

Composite disease indices	Baseline mean values (SD)	Final mean values (SD)	Average change	Effect size (95% CI)	Standardised response mean (95% CI)	Z
DAS28-ESR	6.02 (1.15)	3.96 (1.44)	-2.06	-1.80 (-1.72 to -1.88)	-1.35 (-1.30 to -1.39)	-23.07 (*)
DAS28-CRP	4.38 (0.92)	2.79 (1.12)	-1.60	-1.74 (-1.68 to -1.81)	-1.46 (-1.41 to -1.51)	-24.87 (*)
SDAI	38.19 (12.71)	16.81 (12.11)	-21.38	-1.68 (-1.60 to -1.74)	-1.33 (-1.28 to -1.40)	-22.66 (*)
CDAI	33.12 (12.38)	14.59 (11.67)	-18.53	-1.50 (-1.41 to -1.60)	-1.24 (-1.18 to -1.29)	-21.18 (*)
MOI-RA	51.72 (14.32)	26.97 (14.66)	-24.75	-1.70 (-1.62 to -1.79)	-1.41 (-1.36 to -1.49)	-24.37 (*)
Self-reported questionnaires						
PRO-CLARA	5.31 (1.40)	2.87 (1.60)	-2.44	-1.75 (-1.69 to -1.81)	-1.42 (-1.37 to -1.47)	-24.22 (*)
RAPID3	6.19 (1.70)	3.40 (2.03)	-2.79	-1.64 (-1.58 to -1.71)	-1.26 (-1.20 to -1.33)	-21.52 (*)
PASA	6.19 (1.70)	3.52 (1.86)	-2.67	-1.57 (-1.49 to -1.62)	-1.38 (-1.31 to -1.44)	-5.26 (*)
RADAI	5.64 (1.74)	3.26 (1.92)	-2.37	-1.36 (-1.30 to -1.42)	-1.03 (-0.99 to -1.07)	-17.60 (*)

All significant values (*) were at $p > 0.0001$. DAS28-ESR: Disease Activity Score based on Erythrocyte Sedimentation Rate; DAS28-CRP: Disease Activity Score based on C-Reactive Protein; SDAI: Simple Disease Activity Index; CDAI: Clinical Disease Activity Index; MOI-RA: Mean Overall Index for Rheumatoid Arthritis; PRO-CLARA: Patient-Reported Outcomes-CLinical ARthritis Activity; RAPID 3: Routine Assessment of Patient Index Data 3; PAS: Patient Assessment Score; RADAI: Rheumatoid Arthritis Disease Activity Index.

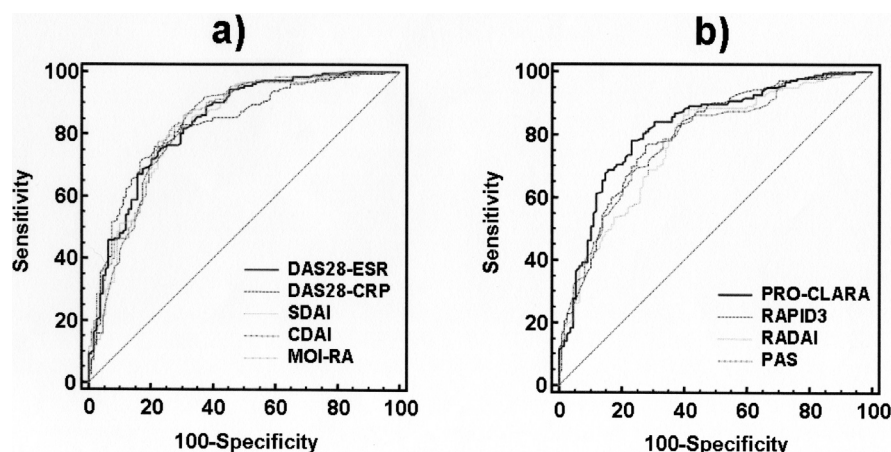


Fig. 3. ROC curves illustrating a) the relationship between sensitivity and complement of specificity (100-specificity) in RA for the self-report questionnaires, and b) traditional composite disease activity indices, using changes in global disease activity as external indicator. The area under the ROC curve (AUC) in this setting can be interpreted as the probability of correctly identifying the improved patients from non-improved. A line that runs diagonally across the figure from lower left to upper right will have an area of 0.5; this represents an instrument that does not discriminate.

Table II. External responsiveness analysis: a comparison of changing scores between patient self-reported questionnaires and traditional composite indices by calculating correlation coefficients.

Self-report questionnaires	r	p-value
PRO-CLARA vs. RAPID3	0.818	<0.0001
PRO-CLARA vs. PAS	0.712	<0.0001
PRO-CLARA vs. RADAI	0.701	<0.0001
RAPID3 vs. PAS	0.891	<0.0001
RAPID3 vs. RADAI	0.818	<0.0001
PAS vs. RADAI	0.787	<0.0001
Traditional composite disease activity indices		
DAS28-ESR vs. DAS28-CRP	0.787	<0.0001
DAS28-ESR vs. SDAI	0.742	<0.0001
DAS28-ESR vs. CDAI	0.739	<0.0001
DAS28-ESR vs. MOI-RA	0.774	<0.0001
DAS28-CRP vs. SDAI	0.661	<0.0001
DAS28-CRP vs. CDAI	0.648	<0.0001
DAS28-CRP vs. MOI-RA	0.625	<0.0001
SDAI vs. CDAI	0.945	<0.0001
SDAI vs. MOI-RA	0.877	<0.0001
CDAI vs. MOI-RA	0.890	<0.0001

PRO-CLARA: Patient-Reported Outcomes-CLinical ARthritis Activity; RAPID 3: Routine Assessment of Patient Index Data 3; PAS: Patient Assessment Score; RADAI: Rheumatoid Arthritis Disease index; DAS28-ESR: Disease Activity Score based on Erythrocyte Sedimentation Rate; DAS28-CRP: Disease Activity Score based on C-Reactive Protein; SDAI: Simple Disease Activity Index; CDAI: Clinical Disease Activity Index; MOI-RA: Mean Overall Index for Rheumatoid Arthritis.

SDAI, the strong correlation noted above is not surprising and may be expected. Although calculated in different ways, changes in the SDAI and in the CDAI were also significantly correlated with mean changes in the MOI-RA ($r=0.877$ and 0.890 , respectively; $p<0.0001$) and in the DAS28-CRP ($r=0.661$ and 0.648 , respectively; $p<0.0001$).

Discussion

This is the first study that compares the responsiveness of a broad array of composite indices and patient self-report questionnaire to measure the activity of RA. We investigated five disease activity indices (DAS28-ESR, DAS28-CRP, SDAI, CDAI, and MOI-RA) and four self-report questionnaires (PRO-CLARA, RAPID3, PAS and RADAI)

in a cohort of established RA patients, receiving DMARDs or a combination of biologic agents and followed for 6 months.

In accordance with Husted *et al.* (42), we calculated the magnitude of the internal responsiveness, using the ES and SRM, and the external responsiveness using ROCs. For the external responsiveness statistics, a health transition index such as the item two on the SF-36 questionnaire that asks about changes in health was used as the reference measure.

In this study, we showed that no significant differences in internal and external responsiveness were found between patient self-report questionnaires and composite indices. The internal responsiveness of the composite measures and self-report questionnaires was large, with SRM and ES ranging from 1.03 (RADAI) to 1.80 (DAS28-ESR). The responsiveness of the PRO-CLARA was equal to the DAS28-ESR, DAS28-CRP, SDAI or MOI-RA, but better than the CDAI. The RADAI and PAS were less responsive than the PRO-CLARA and RAPID3. The area under ROC curve of the PRO-CLARA gives identical results to those provided by other comparator composite indices. The score changes of all combinations were highly correlated ($p<0.0001$).

A systematic literature analysis of studies comparing the psychometric properties of the DAS, DAS28, SDAI and CDAI does not allow for the ranking of these indices in terms of their metrological properties because, except for defining remission, the available studies suggest that the four indices may have similar metrological properties (44). Particularly, the responsiveness was compared in two studies (6, 45), both of which used the ACR response as the reference standard. In one study, one year ES was estimated for the DAS28, SDAI, and CDAI according to the type of ACR response. The sensitivity to change of the DAS28 and the SDAI were comparable, but the CDAI tended to be more responsive, although the difference was difficult to interpret because 95% confidence intervals were not provided (6). The other study found that both the SDAI and the CDAI de-

tected significant differences between non-responders and ACR20/50/70 responders (45). On the contrary, neither indexes significantly differentiated ACR20 and ACR50 responders. The SRMs for the DAS44, DAS28, SDAI, and CDAI were computed in the various ACR responder categories over the two-year follow-up, with slight differences between the indices. For further evidence about their similarities, we showed that the composite disease indices were significantly correlated with each other in score changes. Similarly, Aletaha *et al.* (6) reported that absolute scores of DAS28-ESR, SDAI, and CDAI were significantly correlated, with very similar values of correlation coefficients as our results.

However, although these composite indices are validated and their psychometric properties are known (1-7), concerns have been raised that these indices may not adequately capture all patient-relevant data. Patient self-report questionnaires are an attractive option in a busy medical practice, as the time burden is transferred from the clinician to the patient (5, 15). The validity and usefulness of patient-report outcome (PROs) data in evaluating and monitoring RA patients have been well documented (15-18). Self-report questionnaires have been shown capable of substituting for composite disease activity scores, which were developed primarily for research purposes (46). These questionnaires refrain from formal joint counts and, therefore, all require minimal costs and professional time, which should contribute to their acceptability by practicing physicians (8). Data from patients concerning PRO-CLARA and RAPID3 scores appear adequate to document status and monitor effectiveness of therapies in RA patients, and are substantially more easily obtained than DAS, SDAI, CDAI or MOI-RA (19, 23). Bossert *et al.* (47) assess the validity of the two self-report questionnaires RAPID3 and RADAIS to measure the activity of RA in everyday practice, comparatively to the DAS28, CDAI, and SDAI. The results showed a strong correlation between the RAPID3 and RADAIS scores and three disease activity indices (DAS28, CDAI, and

SDAI), with *p*-values between 0.64 and 0.74, (*p*<0.01). As expected, these correlations were less strong than those found among the three disease-activity indices, which were very closely correlated to one another (*p*>0.87, *p*<0.01). The two self-report questionnaires were also very closely correlated (*p*=0.88, *p*<0.01). These results are also consistent with those of earlier studies (23, 40, 48, 49) and support the validity of patient self-report questionnaires.

Current self-reported questionnaires, therefore, appear to be very useful. However, these scores only include 3 PROs, namely patient assessment of pain, functional disability and/or patient global assessment, and these domains are the only PRO usually reported, while other domains of health appear important from the patient's perspective, such as fatigue, wellbeing and sleep patterns. In this context, through the European League Against Rheumatism (EULAR), an international task force elaborated a new composite response score for clinical trials in RA: the patient-derived Rheumatoid Arthritis Impact of Disease (RAID) score (50, 51). The RAID takes into account pain, functional capacity, fatigue, physical and emotional wellbeing, quality of sleep and coping, and was correlated more strongly to other global measures than to PROs, reflecting single health domains (51). This new score has undergone a successful validation (51), but further data are needed, especially on responsiveness in intervention studies.

All these PRO data have traditionally been collected on paper, but more trials use 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 (52). The introduction of computer touch-screen technology into our clinic routine to capture PRO data in individual RA patients resulted in 100% compliance with completion of all the items of the questionnaire, with good data quality, reliability and score agreement with paper format (52). This favourable reaction is consistent with other studies that have used touch-screen technology to

collect PRO information (53-55). Electronic data collection improves data quality by providing software safeguard against entry omission and inconsistent response sets, and by completely eliminating data entry errors at the research level.

This study has some limits due to specific limitations of each analytic method and the fact that the results cannot be extended beyond RA patients. Furthermore, assessment of patients was performed by different clinician teams, which increases the probability of having significant results by chance.

In conclusion, this is the first study to demonstrate that the patient self-report questionnaire and composite activity scores were comparable in terms of internal and external responsiveness for the detection of rheumatoid disease activity. This appears suitable for clinical decision making, epidemiologic research, and clinical trials. Further longitudinal studies are needed to validate these encouraging results.

Acknowledgements

We thank A. Giardino, A. Ori, L. Zanolli and A. Manfredi for their contribution to the organisation of the study and data management.

The authors wish to thank the other members of the INDICES Study Group: B. Laganà (Roma), G. Varcasia (Mormanno, Cosenza), G. Pomponio (Ancona), F. Mozzani (Parma), R. Scarpa (Napoli), A. Maier (Bolzano), N. Romeo (Cuneo), A. Migliore (Roma), M. Scarpellini (Magenta, Milano), S.M. Corsaro (Napoli), M. Pusceddu (Iglesias, Cagliari), R. Foti (Catania); M. Rotondi (Velletri, Roma), B. Marasini (Rozzano, Milano), G. Ferraccioli (Roma), N. Malavolta (Bologna), L. Sabadini (Arezzo), M. Cimmino (Genova), A. Ricioppo (Vimercate, Milano), G. Triolo (Palermo), M.T. Mascia (Modena), G. Minisola (Roma), K. Botsios (Montebelluna, Treviso), R. Pellerito (Torino), A. Noto (Cosenza), M. Cazzato (Pisa).

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