

Rheumatoid Arthritis disease activity assessment in routine care: performance of the most widely used composite disease activity indices and patient-reported outcome measures

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Abstract. *Background and aim:* To evaluate the convergent and discriminative validity of many continuous composite disease activity indices and patient-reported outcome measures (PROMs) in rheumatoid arthritis (RA). *Methods:* In consecutive RA patients in moderate or high disease activity, according to the Simplified Disease Activity Index (SDAI) definition, were computed four additional composite disease activity indices, the 28-joint Disease Activity Score – erythrocyte sedimentation rate (DAS28-ESR), the Clinical Disease Activity Index (CDAI), the Chronic Arthritis Systemic Index (CASI), and the Mean Overall Index for RA (MOI-RA), and five PROMs, the Patients’ Activity Scale (PAS), the Rheumatoid Arthritis Impact of Disease (RAID), the 5-item RA Disease Activity Index (RADAI-5), the Routine Assessment of Patient Index Data (RAPID3), and the Clinical Arthritis Activity (PRO-CLARA). Spearman’s rho correlation coefficients were determined to assess their convergent validity, and discriminative performance was calculated by the area under the receiver-operating curve (AUC-ROC). The patients’ opinion of their symptomatic status (PASS) was used as the external criterion. *Results:* 246 RA patients with moderate (29.3%) or high disease activity (70.7%) have been assessed. The indices all showed a significant correlation ($p < 0.0001$ for all). Among the composite disease activity indices, the CDAI was the one that showed the best discriminating ability compared to the PASS (AUC = 0.962), while among the PROMs the RAID was the most performing (AUC = 0.879). *Conclusions:* CDAI as composite index of disease activity, and RAID as PROM, are the two instruments with the best performances in relation to PASS. The use of validated disease activity measures can help in clinical practice to adopt treat-to-target strategies in RA patients. (www.actabiomedica.it)

Key words: Rheumatoid arthritis, Disease activity, Composite disease activity indices, Patient-reported outcome measures, Tight control

Introduction

Over the last 20 years, the understanding of the pathophysiological mechanisms underlying rheumatoid arthritis (RA) and its treatment has significantly improved, leading to the possibility of an early

diagnosis, the initiation of intensive therapy, and close monitoring driven by regular measurements of disease activity (1, 2). These advances formed the basis for the formulation of the ‘treat-to-target’ recommendations (3), that should be an essential part of correct patient management (4), as they lead to better

outcomes than standard care (5). Targeted treatment has also been endorsed by the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) and other professional organizations as a fundamental therapeutic strategy and reflects the widely held principles of shared decision-making and individualised treatment choices (4). The accompanying need for close monitoring has two main requirements in routine clinical practice: validated quantitative assessments are necessary to facilitate the continuous monitoring of disease activity over time, and they need to be capable of being rapidly and easily administered and adapted to multiple formats. Composite indices are frequently used in clinical trials and daily practice as they are useful for evaluating treatment responses and making decisions concerning the need to start, adjust or change treatment. The use of disease activity measure such as the 28-joint Disease Activity Score (DAS28) (6), the Simplified Disease Activity Index (SDAI) or the Clinical Disease Activity Index (CDAI) (7), which involve formal joint counts by trained professionals is highly recommended because they capture the most important aspects of RA in a single score.

However, it has recently emerged that patient-reported data can be as useful as any other information when assessing and monitoring patients with RA (8), and that patient-reported outcome measures (PROMs) of functional status may be equally or even more informative than a full joint count for monitoring and prognostic purposes (9). In the current scenario of patient-centered care, rising health-care costs and decreasing resources, PROMs may be a patient-friendly, location-independent, time- and cost-efficient means of monitoring chronic diseases such as RA. More than 30 years of research into rheumatological PROMs has led to the development of various methods covering a broad spectrum of health domains that reflect patients' perspectives concerning the effectiveness of treatments tested in clinical trials. The Patients Activity Scale (PAS) or PAS-II (10), the validated Rheumatoid Arthritis Impact of Disease (RAID) (11), the 5-item RA Disease Activity Index (RADAI-5) (12), the Routine Assessment of Patient Index Data (RAPID) (13), and the Clinical Arthritis Activity (PRO-CLARA) questionnaire (14), are all

well-known examples of PROMs that are used in trials as well as in clinical practice.

As little has been done so far to compare the performance of the most widely used composite disease activity indices and PROMs in evaluating RA disease activity, and the aim of this study was to compare their convergent and discriminative validity in order to facilitate the choice of clinical measures in everyday clinical practice.

Materials and Methods

Setting and inclusion criteria

Consecutive adult-onset RA patients (as defined by the ACR/EULAR classification criteria) (15), with at least moderate disease activity (according to the SDAI definition) (7, 16) were enrolled for a cross-sectional evaluation between January 2016 and March 2020. Patients were recruited from the outpatient clinics of three Italian tertiary rheumatology centers. The exclusion criteria were severe ongoing infections; a history of Parkinson's disease, stroke, depression, fibromyalgia, or Alzheimer's disease.

All of the patients were receiving at least one conventional synthetic disease-modifying anti-rheumatic drug (csDMARD) such as methotrexate, leflunomide, sulphasalazine or hydroxychloroquine, or a biological DMARD (bDMARD).

All the procedures carried out in this study have been conducted in accordance with the 1964 Declaration of Helsinki.

Demographic and anthropometric variables, and comorbidities

A record was made of the patients' age, sex, disease duration (defined as the time since diagnosis)

and educational level (primary school, secondary school, and university), body mass index (BMI) classifying patients in underweight/normal-weight (BMI <25.0 kg/m²), overweight (25.0 kg/m² ≤ BMI <30 kg/m²) or obese (BMI ≥30.0 kg/m²), concomitant treatment with glucocorticoids, csDMARDs or bDMARDs, and comorbidities. The patients'

comorbidity burden was evaluated using the modified Rheumatic Disease Comorbidity Index (mRDCI). The final mRDCI encompasses 13 comorbidities and ranges from 0 to 12 (17).

Laboratory investigations

Blood samples were obtained to evaluate the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels using standard laboratory methods. The presence of IgM rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) was respectively determined by means of nephelometry (Image Beckman) and an immunofluorometric assay (EliA CCP, ImmunoCAP 250, Phadia S.r.l., Italy). The cut-off-value for ACPA positivity was >10 IU/mL as declared in the manufacturer's instructions, and an IgM RF titre of >40 UI/mL was considered positive.

Measures of disease activity

For the purposes of this study, we evaluated 10 recommended composite measures of disease activity, which were then grouped into continuous composite indices, respectively DAS28 (6), SDAI and CDAI (7), Mean Overall Index for RA (MOI-RA) (18), and Chronic Arthritis Systemic Index (CASI) (19), and PROMs, respectively PAS (10), RAID (11), RADAI-5 (12), RAPID-3 (13), and PRO-CLARA (14). All of the assessments were made by experienced physicians. Regular joint count consensus meetings are part of our routine quality control program in order to avoid internal variations among physicians.

Composite disease activity indices

The DAS28-erythrocyte sedimentation rate (DAS28-ESR) includes variables from the ACR core set of measures of RA outcomes (8): it can be used with or without a general health (GH) assessment, which may be replaced by a patient global assessment (PtGA) (20). The DAS28 has been extensively validated, is endorsed by the ACR/EULAR for clinical trials (21) and is often considered the "gold standard" of measuring RA disease activity.

The CDAI combines single measures into an overall continuous measure of RA disease activity. It includes the 28 swollen joint count (SJC), the 28 tender joint count (TJC), the PtGA using a 10 cm visual analogue scale (VAS), and a physician global assessment (PhGA) using a 10 cm VAS. The absence of a laboratory value makes it feasible to use in everyday clinical practice. The disease activity can be classified as remission (≤ 2.8), low (> 2.8 but ≤ 10), moderate (> 10 but ≤ 22), or high (> 22) (7). The CDAI has a linear relationship with the Health Assessment Questionnaire (HAQ) (22). Compared to CDAI, SDAI also includes the CRP value. Disease activity can be classified as remission (≤ 3.3), low (> 3.3 but ≤ 11), moderate (> 11 but ≤ 26), or high (> 26) (9). The SDAI is endorsed by the ACR/EULAR for measuring disease activity in clinical trials, and by EULAR for patient monitoring.

The MOI-RA, a simple index based on the ACR core data set of disease activity and treatment response measures (18), uses mean standardized TJC and SJC (28, 42 or 66/68), physical function (HAQ, 0-3), PtGA and PhGA, a patient pain VAS (0-100 mm), and the ESR (1-100 mm/h).

The CASI includes the Ritchie Articular Index (RAI), a patient pain VAS, the HAQ and the ESR, and was designed based on factorial analyses of 29 variables in order to allow practising rheumatologists to measure disease activity and severity (19).

Patient-reported outcome measures

The PAS is a validated composite patient self-report disease activity scale developed for use in clinical practice, observational studies, and clinical trials (10). It is calculated by multiplying the HAQ by 3.33 and dividing the sum of the pain and global VAS and the HAQ by 3 to obtain a 0-10 scale, a process that should take <15 seconds.

The RAID consists of seven domains (pain, function, fatigue, physical and emotional well-being, sleep disturbances and coping), each of which is evaluated using a single question answered by a 0-10 numerical rating scale (NRS) and has the following weights: pain 21%, functional disability 16%, fatigue 15%, sleep disorders 12%, emotional well-being 12%, physical well-being 12%, and coping 12% (11). The final score ranges

from 0 to 10, with 10 indicating the worst health. A change of at least three points (absolute) or 50% (relative) in the RAID score defines a minimum clinically important Improvement and that a maximum value of 2 defines acceptable status (23). On the basis of distribution of RAID scores in the different disease activity groups, the following cut-off values have been applied: remission ≤ 3 , low disease activity (LDA) >3 but ≤ 4 , moderate disease activity (MDA) >4 but ≤ 6 , and high disease activity (HDA) >6 . Mean RAID scores are significantly different in patients with different disease activity levels (24).

There are five versions of RAPID and we used RAPID-3, which includes physical function, pain and a patient global evaluation. It is mathematically identical to the PAS but has a raw score of 0-30 and an adjusted score of 0-10. The physical function score is converted from 0-3 to 0-10 by multiplying it by 3.33 using a template from the modified HAQ (mHAQ) (25), a 2-sided, single-sheet instrument adapted from the standard HAQ and designed to facilitate review and scoring by health professionals in busy clinical settings. The raw score of 0-30 is divided by three to give an adjusted 0-10 score that can be compared with other RAPID indices. The proposed severity (rather than activity) categories of RAPID-3 on the adjusted 0-10 scale are: very severe >4 , moderate severity 2.01-4.00, not very severe 1.01-2.00, and near remission ≤ 1 (13), and those on the unadjusted 0-30 scale are respectively >12 , 6.1-12.0, 3.1-6.0, and ≤ 3 : an improvement in 3.8/30 units seems to be clinically meaningful (26).

The RADAI-5 has five items rated using a 0-10 Likert-like scale from 0 to 10. It has been shown to measure RA activity with proven reliability and convergent validity (12).

The PRO-CLARA is a short and easily completed self-administered questionnaire that combines three items on physical function (measured using the Recent-Onset Arthritis Disability (ROAD) questionnaire), a self-reported TJC and a PtGA into a single measure of disease activity (14). The ROAD questionnaire, which was developed and validated in Italy (27), can be scored in 15-20 seconds and consists of 12 items that capture a combination of frequent symptoms related to functional abilities, and includes important questions concerning fine movements of the upper

and lower extremities, and activities involving both. The self-reported TJC is evaluated using the RADAI joint list, and the PtGA is scored 0-10 using an NRS to answer the question: "How would you describe your general health today? (0 = very good, 10 = very poor)". The total PRO-CLARA score (range 0-10) is obtained by summing the scores of the three individual measures and dividing the result by three (14).

Statistical analysis

The data were processed using MedCalc statistical software, version 19.0 (Ostend, Belgium), for Windows XP. The general descriptive statistics were summarized using numbers and percentages for categorical variables, and mean values \pm standard deviation (SD) or median values for continuous variables, depending on the distribution of the data as tested using the Shapiro-Wilk test. Between-group differences in proportions were compared using the chi-squared or Fisher's exact test as appropriate. The continuous variables were compared using the Mann-Whitney U test of categories of grouped variables. The construct validity of the of the composite disease activity indices and PROMs in patients with RA, was investigated by correlating the scores of the indices (DAS28, SDAI, CDAI, CASI, MOI-RA, PRO-CLARA, RADAI-5, RAI, RAID, and RAPID-3) one versus the other. Rho was interpreted as follows: between 0.1-0.29 no or negligible correlation; 0.30-0.49 poor correlation, 0.50-0.69 moderate correlation, 0.70-0.89 close correlation, and 0.9-1.0 very close correlation. Due to multiple comparisons with an increasing risk of type I errors, the level of statistical significance was set at 0.01.

The discriminative accuracy of the composite measures, using the patient acceptable symptom state (PASS) as external criterion, was assessed by means of receiver operating characteristic (ROC) curve analysis. The patients were divided into two groups on the basis of predefined PASS cut-off values. PASS was recorded as a "yes" or "no" answer to the anchor question: "Considering all the different ways your disease is affecting you, if you were to stay in this state for the next few months, do you consider that your current state is satisfactory?" (28). Area under the curve (AUC)

values of 0.5-0.7 indicate poor accuracy, those of 0.7-0.9 moderate accuracy, and those of >0.9 a high degree of accuracy (29). ROC curves were computed using 1,000 boot-strapped samples, non-parametric re-sampling, and the bias-corrected, accelerated method of computing 95% confidence intervals (CIs). The Wilcoxon's non-parametric signed ranks test was used to calculate and compare the areas under the ROC curves (AUC-ROCs) derived from the patient sample (30). A p value of <0.05 was considered statically significant for all the tests.

Results

The study involved 246 RA patients: 203 women (82.5%) and 43 men (17.5%) with a mean age of 55.6 ± 12.6 years, a mean disease duration of 8.3 ± 3.4 years, and a mean BMI of 26.7 ± 4.1 ; 69.4% were RF positive and 58.8% ACPA positive. All the patients were treated with a least one csDMARD, 55 (29.6%) were also receiving a bDMARD (15 patients were receiving adalimumab, 14 etanercept, 11 golimumab, 9 abatacept, 4 tocilizumab, and 2 infliximab). Thirty-two patients (17.2%) were taking oral corticosteroids at a mean prednisone or equivalent dose of 4.9 mg/day (range 2.5-20 mg/day), and 113 (60.8%) were prescribed non-steroidal anti-inflammatory drugs (NSAIDs) on demand. Of the 246 subjects, 145 (58.9%) reported one or more medical comorbidities, mainly cardiovascular (22.4%), respiratory (21.1%) and metabolic disorders (19.9%).

Table 1 summarizes the patients' demographic and clinical characteristics, including the values of all the composite disease activity indices and PROMs investigated. A normal distribution was observed for all indices. A highly significant correlation was found among all the indices ($p < 0.0001$ for all) (Table 2).

Fifty-five RA patients out of 246 (22.4%) resulted in PASS. In accordance with the inclusion criterion for SDAI, 70.7% of patients had high disease activity, while 29.3% had moderate disease activity. The mean SDAI was 39.01 ± 13.25 . Using DAS28-ESR, 78% of patients were in high disease activity, 22% in moderate disease activity (mean DAS28-ESR 5.82 ± 1.03). Employing CDAI this percentage was similar to that

found with SDAI (high disease activity in 69.5% and moderate disease activity in 30.5%, mean CDAI 32.28 ± 13.85).

Analyzing the discriminative power of each tool compared to PASS, the AUC-ROCs were good for all composite disease activity indices, respectively 0.900 for DAS28-ESR, 0.962 for CDAI, 0.927 for SDAI, 0.910 for MOI-RA, and 0.854 for CASI; and for PROMs, respectively 0.845 for PAS, 0.879 for RAID, 0.842 for RAPID-3, 0.815 for RADAI-5, and 0.835 for PRO-CLARA (Table 3, Figure 1). The discriminative power of CDAI was very good, with an AUC that was significantly different from that of DAS28-ESR (z statistic = 3.29; $p = 0.001$), MOI-RA (z statistic = 2.93; $p = 0.003$), CASI (z statistic = 3.61; $p = 0.0003$), and SDAI (z statistic = 3.95; $p = 0.003$). The RAID questionnaire performed significantly better than RADAI-5 (z statistic = 2.03; $p = 0.041$) in discriminating patients with moderate and high disease activity (Table 4).

Discussion

In this study it was shown that, although the performance of the various composite disease activity indices and PROMs are largely overlapping, the CDAI as composite disease activity index, and RAID as PROM, are the ones that better distinguish PASS positive patients. Consequently, these two indices could represent the rheumatologist's core business in assessing disease activity in RA patients.

The CDAI has the great advantage of not including acute phase reactants and is calculated with the simple algebraic sum of SJC, TJC, PtGA and PhGA. From this point of view it is very useful in daily clinical practice, and can be calculated at any time. Its validity has also been studied in relation to radiological progression (31). The simplicity of administration, the ease of calculation, the validity, and the availability of cut-offs that distinguish the status of disease activity, are the characteristics that make RAID a very useful PROM in the evaluation of RA (11, 24).

Quantitative assessments of RA are different from those of many other clinical conditions because, there is no single "gold standard" diagnostic, prognostic or

Table 1. Demographic and clinical characteristics of the cohort (246 patients)

	Mean	Median	SD	25 - 75 P
Age, years	55.61	56.50	12.64	47.00 - 65.00
Disease duration, years	8.28	9.00	3.42	5.00 - 11.00
BMI, kg/m ²	26.67	26.15	4.08	19.00 - 35.00
mRDCI (0-12)*	1.64	1.00	1.56	0.00 - 2.00
CRP, mg/dL	4.95	3.94	4.14	2.50 - 5.90
ESR, mm/h	43.11	39.00	16.93	32.00 - 50.00
28-SJC (0-28)	7.92	6.50	5.55	4.00 - 11.00
28-TJC (0-28)	11.16	10.00	6.63	6.00 - 15.00
GH (0-100)	66.17	70.00	21.67	50.00 - 80.00
HAQ-DI (0-3)	1.38	1.30	0.60	0.92 - 1.80
mHAQ (0-3)	1.35	1.20	0.59	0.92 - 1.80
ROAD (0-10)	4.28	3.95	2.02	2.71 - 5.83
PhGA (0-10)	7.10	7.00	1.71	6.00 - 8.00
PtGA (0-10)	6.03	6.00	2.24	5.00 - 8.00
RAI (0-78)	25.38	24.00	13.58	12.00 - 33.00
Self-reported TJC (0-10)	4.40	4.20	1.62	3.30 - 5.30
<i>Composite disease activity indices</i>				
DAS28-ESR (0-9.84)	5.82	5.90	1.03	4.92 - 6.47
CDAI (0-76)	32.28	30.00	13.85	21.00 - 41.00
SDAI (0-86)	39.01	40.48	13.25	26.66 - 45.76
MOI-RA (0-100)	50.45	49.80	14.18	40.34 - 60.85
CASI (0-74)	29.15	28.79	9.49	22.12 - 35.79
<i>Patient-reported outcome measures</i>				
PAS (0-10)	6.02	6.06	1.70	4.77 - 7.24
RAID (0-10)	6.06	6.13	1.52	4.96 - 7.18
RADAI-5 (0-10)	5.74	5.75	3.03	4.31 - 6.89
RAPID-3 (0-10)	6.10	6.11	1.69	4.78 - 7.44
PRO-CLARA (0-10)	4.87	4.77	1.50	3.79 - 5.97

Abbreviations: SD = standard deviation; P = percentile; BMI = body mass index; mRDCI = modified Rheumatic Disease Comorbidity Index; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; 28-SJC = 28-swollen joint count; 28-TJC: 28-tender joint count; PhGA = physician global assessment; PtGA = patient global assessment; RAI = Ritchie Articular Index; HAQ = Health Assessment Questionnaire; mHAQ = modified Health Assessment Questionnaire; ROAD = Recent-Onset Arthritis Disability; DAS28 = 28-joint Disease Activity Score; CDAI = Clinical Disease Activity Index; SDAI = Simplified Disease Activity Index; MOI-RA = Mean Overall Index for Rheumatoid Arthritis; CASI = Chronic Arthritis Systemic Index; PAS = Patient Activity Scale; RAID = Rheumatoid Arthritis Impact of Disease; RADAI-5 = 5-item Rheumatoid Arthritis Disease Activity Index; RAPID-3 = Rheumatoid Arthritis Disease Activity Index 3; PRO-CLARA = Patient-Reported Outcome Clinical Arthritis Activity.

*the mRDCI is calculated as 1 point for lung disease, 2 points for (myocardial infarction, other cardiovascular diseases, or stroke), 1 point for hypertension and 1 point for ulcer or other gastrointestinal diseases, 2 points for kidney disease and 1 if body mass index (BMI) is >30 kg/m² or 2 if BMI is >35 kg/m², and 1 for each of diabetes, fracture, depression and cancer.

monitoring measure that can be applied to all patients (32). The involvement of multiple health domains in RA has led to the increasing use of composite indices consisting of different quantitative measures that have

allowed clinical assessments to be made by reducing measurement error, providing objective means of evaluation, and improving the analysis and interpretation of clinical trials of new DMARDs (33).

Table 2. Correlation coefficients (rho, Spearman's rank correlation coefficient) between the composite disease activity indices and the patient-reported outcome measures

	CASI	SDAI	MOI-RA	CDAI	PRO-CLARA	RADAI-5	RAI	RAID	RAPID-3
DAS28-ESR	0.531 <0.0001	0.791 <0.0001	0.837 <0.0001	0.850 <0.0001	0.565 <0.0001	0.632 <0.0001	0.656 <0.0001	0.666 <0.0001	0.660 <0.0001
CASI		0.545 <0.0001	0.684 <0.0001	0.517 <0.0001	0.583 <0.0001	0.495 <0.0001	0.408 <0.0001	0.533 <0.0001	0.705 <0.0001
SDAI			0.793 <0.0001	0.854 <0.0001	0.595 <0.0001	0.581 <0.0001	0.654 <0.0001	0.620 <0.0001	0.599 <0.0001
MOI-RA				0.837 <0.0001	0.695 <0.0001	0.796 <0.0001	0.588 <0.0001	0.683 <0.0001	0.876 <0.0001
CDAI					0.574 <0.0001	0.617 <0.0001	0.754 <0.0001	0.683 <0.0001	0.618 <0.0001
PRO-CLARA						0.643 <0.0001	0.476 <0.0001	0.532 <0.0001	0.673 <0.0001
RADAI-5							0.418 <0.0001	0.580 <0.0001	0.823 <0.0001
RAI								0.566 <0.0001	0.402 <0.0001
RAID									0.608 <0.0001

Abbreviations: CASI = Chronic Arthritis Systemic Index; SDAI = Simplified Disease Activity Index; MOI-RA = Mean Overall Index for Rheumatoid Arthritis; CDAI = Clinical Disease Activity Index; PRO-CLARA = Patient-Reported Outcome Clinical Arthritis Activity; RADAI-5 = 5-item Rheumatoid Arthritis Disease Activity Index; RAI = Ritchie Articular Index; RAID = Rheumatoid Arthritis Impact of Disease; RAPID-3 = Rheumatoid Arthritis Disease Activity Index 3; DAS28 = 28-joint Disease Activity Score; ESR = erythrocyte sedimentation rate.

Table 3. Area under the receiver operating characteristic curve values for each composite disease activity index and patient-reported outcome measure distinguishing patients according to the patient acceptable symptom state (PASS)

<i>Composite disease activity indices</i>	AUC	SE ^a	95% CI ^b
DAS28-ESR	0.900	0.021	0.856 - 0.935
CDAI	0.962	0.011	0.930 - 0.982
SDAI	0.927	0.019	0.884 - 0.941
MOI-RA	0.910	0.020	0.867 - 0.942
CASI	0.854	0.029	0.803 - 0.895
<i>Patient-reported outcome measures</i>			
PAS	0.845	0.028	0.793 - 0.888
RAID	0.879	0.024	0.832 - 0.917
RAPID-3	0.842	0.027	0.791 - 0.886
RADAI-5	0.815	0.029	0.761 - 0.862
PRO-CLARA	0.835	0.027	0.783 - 0.879

Legend: a = Hanley & McNeil, 1982; b = Binomial exact.

Abbreviations: AUC = area under the curve; SE = standard error; CI = confidence interval; DAS28 = 28-joint Disease Activity Score; ESR = erythrocyte sedimentation rate; CDAI = Clinical Disease Activity Index; SDAI = Simplified Disease Activity Index; MOI-RA = Mean Overall Index for Rheumatoid Arthritis; CASI = Chronic Arthritis Systemic Index; PAS = Patient Activity Scale; RAID = Rheumatoid Arthritis Impact of Disease; RAPID-3 = Rheumatoid Arthritis Disease Activity Index 3; RADAI-5 = 5-item Rheumatoid Arthritis Disease Activity Index; PRO-CLARA = Patient-Reported Outcome Clinical Arthritis Activity.

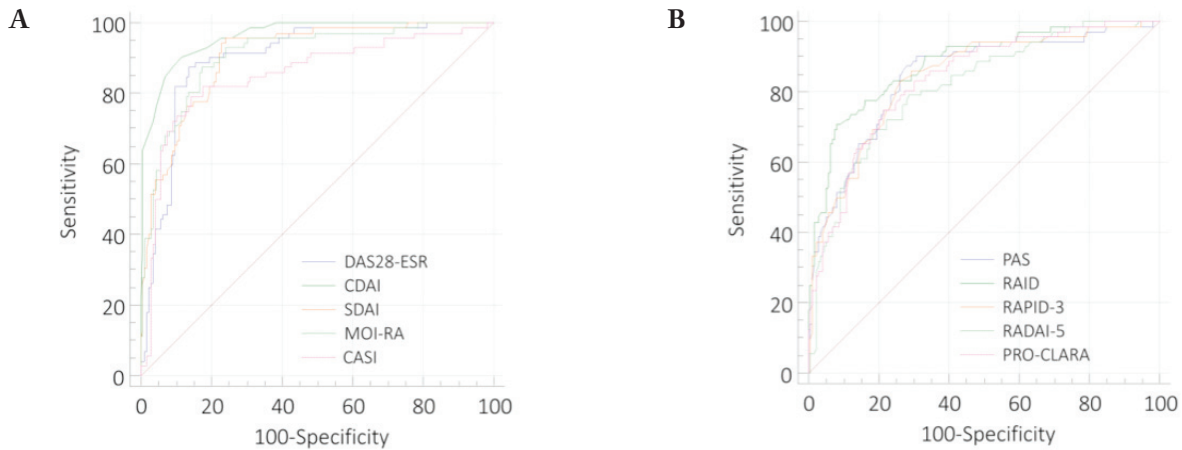


Figure 1. Receiver operating characteristic curves comparing the discriminative power of the composite measures in identifying rheumatoid arthritis patients with moderate/high disease activity. The curves show the relationship between sensitivity and the complement of specificity (100-specificity) for the composite disease activity indices (A) and/or the patient-reported outcome measures (B), using the patient acceptable symptom state (PASS) as external criterion.

Abbreviations: DAS28 = 28-joint Disease Activity Score; ESR = erythrocyte sedimentation rate; CDAI = Clinical Disease Activity Index; SDAI = Simplified Disease Activity Index; MOI-RA = Mean Overall Index for Rheumatoid Arthritis; CASI = Chronic Arthritis Systemic Index; PAS = Patient Activity Scale; RAID = Rheumatoid Arthritis Impact of Disease; RAPID-3 = Rheumatoid Arthritis Disease Activity Index 3; RADAI-5 = 5-item Rheumatoid Arthritis Disease Activity Index; PRO-CLARA = Patient-Reported Outcome Clinical Arthritis Activity.

Although very different in nature and initially intended for use in clinical trials (3, 4, 16, 33-35), these indices have been increasingly adopted in everyday clinical practice, although they may not be equally appropriate as some require the use of formal joint counts, and others require the use of calculators or cannot be used for immediate decision making because of missing laboratory results. In order to overcome such drawbacks and given the increasing emphasis on patient perspectives when considering priorities and making treatment choices, PROMs have become a core part of the routine assessment of RA and an endpoint in clinical trials and observational studies, and their use is widely supported by international organizations and professional bodies such as the European Patients' Academy on Therapeutic Innovations and the US Patient-Centered Outcomes Research Institute (PCORI), as well as by regulatory agencies such as the Food and Drug Administration and the European Medicines Agency, all of which recognize the usefulness of having patients provide direct feedback about their disease (3, 4, 36).

Three studies investigated whether such PROMs or the SDAI, CDAI and DAS28 distinguished patients with or without treatment changes (37-39), all of which used the AUC-ROC to demonstrate their good performance. The first showed that they were similarly capable of distinguishing patients whose infliximab dose had or had not been increased (37). The second found that the SDAI tended to discriminate patients with and without a change in DMARDs better than the DAS28 (37). The third showed that, the responsiveness of PRO-CLARA was equal to that of the DAS28-ESR, DAS28-CRP, SDAI or MOI-RA, but better than the CDAI (39).

Our study is the first to compare the concurrent validity and discriminative performance of 10 of the 63 currently available instruments for measuring RA disease activity (35): five composite disease activity indices and five PROMs. The analysis of convergent validity showed a significant correlation between the ten indices in terms of absolute scores.

Comparing the AUC-ROCs, this detailed study showed that the CDAI is the most efficient of the

Table 4. Comparisons between the areas under the receiver operating characteristic curve for each composite disease activity index and for each patient-reported outcome measure

Comparison	Difference between areas	SE ^a	95% CI	z statistic	p
DAS28-ESR vs CDAI	0.061	0.018	0.025 - 0.090	3.298	0.001
DAS28-ESR vs SDAI	0.007	0.023	-0.039 - 0.053	0.303	0.761
DAS-28-ESR vs MOI-RA	0.009	0.020	-0.030 - 0.049	0.465	0.641
DAS28-ESR vs CASI	0.046	0.034	-0.020 - 0.114	1.360	0.173
CDAI vs SDAI	0.054	0.018	0.018 - 0.090	2.295	0.003
CDAI vs MOI-RA	0.052	0.017	0.017 - 0.087	2.930	0.003
CDAI vs CASI	0.108	0.029	0.049 - 0.167	3.619	0.003
SDAI vs MOI-RA	0.002	0.023	-0.043 - 0.048	0.096	0.923
SDAI vs CASI	0.053	0.032	-0.008 - 0.117	1.680	0.093
MOI-RA vs CASI	0.056	0.030	-0.003 - 0.116	1.848	0.064
PAS vs RAID	0.034	0.030	-0.025 - 0.094	1.136	0.256
PAS vs RAPID-3	0.002	0.010	-0.017 - 0.022	0.236	0.813
PAS vs RADAI-5	0.029	0.025	-0.019 - 0.078	1.175	0.239
PAS vs PRO-CLARA	0.009	0.032	-0.054 - 0.073	0.239	0.769
RAID vs RAPID-3	0.036	0.029	-0.021 - 0.095	1.246	0.212
RAID vs RADAI-5	0.064	0.031	0.002 - 0.126	2.037	0.041
RAID vs PRO-CLARA	0.044	0.032	-0.020 - 0.108	1.343	0.179
RAPID-3 vs RADAI	0.027	0.023	-0.018 - 0.072	1.167	0.243
RAPID-3 vs PRO-CLARA	0.007	0.032	-0.055 - 0.069	0.225	0.822
RADAI-5 vs PRO-CLARA	0.019	0.032	-0.044 - 0.084	0.606	0.544

Legend: *a* = Hanley & McNeil, 1983.

Abbreviations: SE = standard error; CI = confidence interval; DAS28 = 28-joint Disease Activity Score; ESR = erythrocyte sedimentation rate; CDAI = Clinical Disease Activity Index; SDAI = Simplified Disease Activity Index; MOI-RA = Mean Overall Index for Rheumatoid Arthritis; CASI = Chronic Arthritis Systemic Index; PAS = Patient Activity Scale; RAID = Rheumatoid Arthritis Impact of Disease; RAPID-3 = Rheumatoid Arthritis Disease Activity Index 3; RADAI-5 = 5-item Rheumatoid Arthritis Disease Activity Index; PRO-CLARA = Patient-Reported Outcome Clinical Arthritis Activity.

composite disease activity indices, while RAID is the most performing of the PROMs.

In addition to the specific limitations of each analytical method, our study has some other limitations. The first is the “circularity” of the approach, i.e. the same parameters have entered into the calculation of different indices of disease activity.

A second limit may be the use of the SDAI definition as inclusion criterion for the presence of at least moderate disease activity. The definition of disease activity categories is not completely overlapping between the composite indices and therefore, SDAI could identify patients who, using DAS28 for example, may not be in a moderate disease activity. However, SDAI represents

the composite index supported by both EULAR and ACR for the evaluation of disease activity both in clinical trials and in daily clinical practice, due to its psychometric properties and ease of use (16).

A third limit is the application of PASS in patients with moderate and high disease activity. As was expected, only a minority of patients were in an acceptable RA status. Even the PASS itself as external criterion can be somewhat criticized; however it represents a relevant dichotomous clinical cut-off that represents the patient’s point of view (“feeling good”). PASS has already been widely used in rheumatology, and Outcome Measures in Rheumatology (OMER-ACT) endorsed it.

A fourth limit is the cross-sectional design, which does not allow any evaluation of the indices' sensitivity to change.

Furthermore, in this study, patients with concomitant fibromyalgia, diagnosed according to ACR 2016 criteria (42), were excluded. In accordance with these criteria, the diagnosis of fibromyalgia is independent of the coexistence of other conditions. Fibromyalgia may be a comorbidity, or a continuous phenotypic spectrum associated with variations in central pain processing, and it has been estimated that from 10 to 15% of RA patients have a fibromyalgic RA (16). Fibromyalgic RA is generally characterized by greater pain, higher disease activity scores, and poorer mental health.

In conclusion, although there is currently no ideal measure of disease activity, based on the results of our study, CDAI and RAID are the ones with the best performances in relation to PASS (and SDAI considering the inclusion criteria).

The use of validated disease activity measures can help in clinical practice to adopt treat-to-target strategies in RA patients.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Ethics approval: The procedures conducted in the study were approved by the local Ethics Committee (Comitato Unico Regionale – number 2015 0458 AS, Comitato Etico Messina – number 48/19, Comitato Etico Milano Area 1 453 del 4/6/2015).

Consent to participate: All patients agreed to participate in the study by signing informed consent.

Availability of data and material: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions: FS, MDC, SF, DM, FA, and PSP performed the clinical data collection. FS drafted the article and performed the statistical analysis. FS and PSP gave substantial contributions to the conception and design of the work. All authors read and approved the final manuscript.

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- Score-II (PASII), Routine Assessment of Patient Index Data (RAPID), Rheumatoid Arthritis Disease Activity Index (RADAI) and Rheumatoid Arthritis Disease Activity Index-5 (RADAI-5), Chronic Arthritis Systemic Index (CASI), Patient-Based Disease Activity Score With ESR (PDAS1) and Patient-Based Disease Activity Score without ESR (PDAS2), and Mean Overall Index for Rheumatoid Arthritis (MOI-RA). *Arthritis Care Res (Hoboken)* 2011; 63(Suppl 11): S14-S36.
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