Joint Bone Spine xxx (2017) xxx–xxx

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Original article

Validity of the rheumatoid arthritis impact of disease (RAID) score and definition of cut-off points for disease activity states in a population-based European cohort of patients with rheumatoid arthritis

Fausto Salaffi [a], Marco Di Carlo [a,*], Jelena Vojinovic [b], Angela Tincani [c], Alberto Sulli [d], Stefano Soldano [d], Laura Andreoli [c], Francesca Dall'Ara [c], Ruxandra Ionescu [e], Katarina Simić Pašalić [f], Ineta Balčune [g], Iván Ferraz-Amaro [h], Malgorzata Tlustochowicz [i], Irena Butrimienė [j], Egle Punceviciene [k], Natalia Toroptsova [l], Simeon Grazio [m], Jadranka Morović-Vergles [n], Pavol Masaryk [o], Kati Otsa [p], Miguel Bernardes [q], Vladimira Boyadzhieva [r], Maurizio Cutolo [d]

[a] *Rheumatology department, polytechnic university of Marche, "Carlo Urbani" hospital, via Aldo Moro 25, 60035 Jesi Ancona, Italy*
[b] *Department pediatric rheumatology, clinical center, medical faculty, university of Nis, Bul Zoran Djindjic 81, 18000 Nis, Serbia*
[c] *Division of rheumatology, department of clinical and experimental science, university of Brescia, ASST, Spedali Civili di Brescia, piazzale Spedali Civili 1, 25123 Brescia, Italy*
[d] *Research laboratory and division of clinical rheumatology, department of internal medicine, university of Genova, IRCCS San Martino, Largo R. Benzi 10, 16132 Genova, Italy*
[e] *Department of internal medicine and rheumatology, Sf. Maria Hospital, university of medicine and pharmacy "Carol Davila", boulevard Ion-Mihalache 37-39, sector 1, 020021 Bucharest, Romania*
[f] *Institute of rheumatology, Resavska 69, 11000 Belgrade, Serbia*
[g] *Division of rheumatology, Paula-Stradina clinical hospital, Pilsoņu 13, Nr. 26, corpuss 10, LV-1001, Riga, Latvia*
[h] *Servicio de reumatología, hospital universitario de Canarias, Planta 5, Ofra s/n La Cuesta, 38320 Santa Cruz de Tenerife, Spain*
[i] *Military institute of medicine, department of internal medicine and rheumatology, Szaserów 128, 04-141, Warsaw, Poland*
[j] *Vilnius university, rheumatology center Santariskiu 2, 08406 Vilnius, Lithuania*
[k] *RSI Center of inovative medicine, Santariskiu 5, 08410 Vilnius, Lithuania*
[l] *Scientific research institute of rheumatology "V. A. Nasonova", Karshirskoe shosse 34A, 115522 Moscow, Russia*
[m] *Department of rheumatology, Sisters of Mercy clinical hospital center university, physical and rehabilitation medicine, Vinogradska 29, 10000 Zagreb, Croatia*
[n] *Department for clinical immunology and rheumatology, clinical hospital Dubrava, school of medicine, university of Zagreb, Avenija Gojka Šuška 6, 10000 Zagreb, Croatia*
[o] *National institute of rheumatic diseases, Nabrezie Ivana Krasku 4, SK-921 01 Piestany, Slovakia*
[p] *Department of rheumatology, East Tallinn central hospital, Ravi street 18, 10138 Tallinn, Estonia*
[q] *Rheumatology department of São João hospital center and faculty of medicine of university of Porto (FMUP), Alameda Professor Hernani Monteiro, 42000 Porto, Portugal*
[r] *Medical university-Sofia, UMHAT "St. Iv. Rilski", department of rheumatology, Urvich St. 13, 1612 Sofia, Bulgaria*

ARTICLE INFO

Article history:
Accepted 14 May 2017
Available online xxx

Keywords:
Rheumatoid arthritis
RAID
Disease activity
Patient-reported outcomes

ABSTRACT

Objectives: To assess the validity of the rheumatoid arthritis impact of disease (RAID) for measuring disease activity of rheumatoid arthritis (RA) and to determine cut-off values for defining the disease activity states.
Methods: A total of 622 RA patients from an European database have been included. Cross-validation was based on assessment of convergent and discriminant validity. Optimal cut-offs were determined against external criteria by calculating the respective 25th and 75th percentiles mean values of RAID. External criteria included definitions for remission (REM), low disease activity (LDA), moderate disease activity (MDA) and high disease activity (HDA), cut-offs of the 28-joint disease activity score-C-reactive protein (DAS28-CRP) score.

* Corresponding author.
E-mail address: dica.marco@yahoo.it (M. Di Carlo).

http://dx.doi.org/10.1016/j.jbspin.2017.05.020

Results: The RAID showed a moderate degree of correlation with respect to DAS28-CRP (rho = 0.417; $P < 0.0001$). The receiver operating characteristic (ROC) curves to discriminate the ability of RAID to distinguish patients with active and non-active disease was very good with an area under the curve (AUC) of 0.847 (95% confidence interval [CI]: 0.816 to 0.878; $P < 0.0001$). Based on the distributions of RAID in the different disease activity groups, we propose the following cut-off values for REM: RAID ≤3; for LDA: RAID >3 and ≤4; for MDA: RAID >4 and ≤6; for HDA: RAID >6. Mean RAID differed significantly between patients classified as REM, LDA, MDA or HDA ($P = 0.001$).
Conclusions: The cut-offs revealed good measurement characteristics in cross-validation analysis, had great discriminatory performance in distinguishing patients with different levels of disease activity and are suited for widespread use in everyday practice application and research.

1. Introduction

In the last years, the management of rheumatoid arthritis (RA) has been shifted towards a more patient-centered perspective of the disease adopting dedicated instruments such as the patient-reported outcomes (PROs) [1]. Through PROs, patients themselves can tell about the perception of their health, disease or treatment. The European league against rheumatism (EULAR), the American college of rheumatology (ACR) and the outcome measures in rheumatology (OMERACT) have well outlined the importance PROs in addition to physician assessed outcomes, disease progression instruments and responsiveness measures in the management of RA [2–4]. The escalating importance of PROs is proved also by a Food and Drug Administration (FDA)'s issuance of few years ago [5]. Besides the ability to discriminate between responders and non-responders, validated self-reporting instruments are very easy to administer, have no cost, are non invasive and they pass the OMERACT quality filter (truth, discrimination and feasibility) [6]. Self-report questionnaires provide scores based mainly on three patient-reported domains, such as physical function, pain intensity and overall assessment of disease. In RA, PROs allow a quantitative assessment of disease activity founded on patient-reported data, without requiring routinely joint counts. Although these tools are designed for monitoring patients in everyday clinical practice, they can not be considered a replacement of the clinical examination. Important instruments but rarely used in studies, include the RA disease activity index (RADAI) [7] and the newly adapted RADAI-5 [8], the routine assessment of patient index data (RAPID) [9], the patients' activity scale (PAS) or PAS-II [10] and the clinical arthritis activity (PRO-CLARA) questionnaire [11].

Recently, the EULAR endorsed the development of a new, self-reported questionnaire, called RA, impact of disease (RAID) [12–14]. RAID is a composite measure that reflecting the disease activity and the impact of RA from the patient's perspective, consists in the evaluation of seven domains (pain, function, fatigue, physical and psychological well-being, sleep disturbance and coping). Each domain has a specific weight assigned during the development survey. The final score is a continuous variable ranging from 0 (best) to 10 (worst). The strengths of RAID are its simplicity, since it can be computed without blood tests or physician's assessment and the quick fulfillment. Consequently, this questionnaire can be achieved at short intervals (weekly or monthly), even at home with the assistance of the information and communication technologies [15]. An international study in 2011 provided evidences on the construct validity, reliability and responsiveness of this tool [13].

To date, the major limitation for the routinely use of RAID in trials and clinical practice is the lack of definition of disease activity cut-offs. For the interpretation of a clinical index, cut-offs are essential to define the level of disease activity in a single time point ("disease activity status") but also to assess changes after therapeutic interventions ("response criteria"). Thus, cut-offs can enhance the usefulness of a tool born to allow a closer monitoring of RA and could represent a selection criteria for patient participation in research studies. A regular self-evaluation with RAID may also ensure prospective flare detection, although other approaches (questionnaire completed during physician visits) have been suggested to identify flares retrospectively [16,17]. Dougados et al. gave the following keys to understand this tool: a change of at least 3 points (absolute improvement) or 50% (relative improvement) from baseline value is able to define a minimum clinically important improvement (MCII), while a maximal value of 2 characterizes the patient acceptable symptom state (PASS) [18].

Keeping in mind these considerations, this study aimed to evaluate the construct validity of the RAID for measuring RA disease activity defining the cut-off values for remission disease (REM), low disease activity (LDA), moderate disease activity (MDA) and high disease activity (HDA), comparatively to the 28-joints disease activity score-C-reactive protein (DAS28-CRP).

2. Methods

2.1. Study population and design

This was a post-hoc analysis of cross-sectional study which involved rheumatologists and patient representatives (PARE) organizations from 13 European countries (Bulgaria, Croatia, Estonia, Italy, Lithuania, Latvia, Poland, Portugal, Romania, Russia, Serbia, Slovakia and Spain), oriented to construct and cross-culturally validate a PRO questionnaire for RA patients to self-estimate the risk for vitamin D insufficiency/deficiency (D-PRO) [19]. The study was performed in accordance with the rules of good clinical practice and Helsinki declaration and approved by the research ethics committee (Comitato Etico Spedali Civili di Brescia, Italy, protocol number 1265). All subjects gave written informed consent to participate in the study. The inclusion criteria in this research were the following: age between 25–65 years, RA diagnosis established by ACR/EULAR criteria [20] at least one year prior to study entry, stable treatment with conventional synthetic disease modifying anti-rheumatic drugs (DMARDs) (i.e. methotrexate, leflunomide, hydroxychloroquine) or biologic agents for at least 3 months prior to enrollment and glucocorticoids dosage ≤ 7.5 mg/day of prednisone or equivalent for at least one month prior to enrollment.

2.2. Laboratory investigations

Baseline blood samples were obtained to evaluate the CRP (normal values ≤ 0.80 mg/dL) level, using standard laboratory methods, the presence of IgM-rheumatoid factor (RF) determined by nephelometric method and anti-citrullinated protein antibodies (ACPA) determined by immunofluorometric assay. ACPA positivity was considered for values > 10 IU/mL, according to the manufacturer's

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instructions, as well as RF presence was attributed for concentrations > 40 UI/mL.

2.3. Clinical assessment

In all eligible RA patients, according to detailed study protocol and predefined case reported form (CRF) we collected: demographic data, patient-centered measures and evaluated disease activity using DAS28-CRP (given that CRP was only acute phase reactant available in the cross-sectional cohort). The DAS28-CRP combines information from the 28 tender and swollen joint count, the CRP (mg/dL) and the patient's general health status (PtGH), measured with a visual analogue scale (VAS) of 100 mm [21–23]. According to EULAR criteria, the disease activity was interpreted as remission (DAS28 ≤2.6), low disease activity (DAS28 > 2.6 and ≤ 3.2), moderate disease activity (DAS28 > 3.2 and ≤ 5.1) or as high disease activity (DAS28 > 5.1) [24–26].

2.4. Patient-centered measures

All patients were requested to complete the health assessment questionnaire-disability index (HAQ-DI) [27] and the RAID [12].

The HAQ-DI assesses the degree of difficulty a person experiences in accomplishing tasks in eight functional areas of the daily life. For each item, patients are asked to rate level of difficulty over the past week on a 4-point scale. The final disability dimension score ranges from 0 to 3, with a higher score indicating more disability.

The RAID is developed, translated and validated across several countries, it is free of charge and short, making it feasible and widely applicable [12,13]. As sketched above, it measures seven domains, each one scored on 0–10 numerical rating scale, that are perceived by patients to be particularly important for their health. Each domain has the following weight: pain 0.21, functional disability 0.16, fatigue 0.15, sleep problems 0.12, emotional well-being 0.12, physical well-being 0.12 and coping 0.12. The final value has a range from 0–10, with higher values representing a worse health.

2.5. Statistical analysis

Continuous data were presented as means with standard deviations (SDs) or medians and interquartile ranges (IQR), depending on their distribution (evaluated through the Kolmogorov–Smirnov test). Categorical data were presented as proportions. Demographic and clinical measures were compared using Mann–Whitney U test for continuous variables and chi^2 analysis for discontinuous variables. *P* values below 0.05 were regarded as statistically significant.

The construct validity of the RAID was investigated in two ways. Firstly, we explored the convergent validity of the questionnaire. Convergent validity examines the extent to which a particular measurement relates to other scales that are believed to assess the same construct. In the absence of a true "gold standard" against which to assess criterion validity of the RAID, we compared this questionnaire with commonly used external measurements likely to reflect the impact of RA. Thus, correlation between the RAID and the HAQ-DI and the DAS28-CRP score was measured. Spearman's correlation coefficient was used to test convergent validity of the questionnaire. Secondly, we used the receiver operating characteristic (ROC) curve analysis to explore the discriminative accuracy of the RAID scores, to distinguish patients with active (group A) and non-active disease (group B). The DAS28 EULAR criteria were applied as external criterion [24]. Since ROC analysis requires external criteria to be dichotomous, REM and LDA patients were grouped together as "overall" LDA. 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. Values for the AUC-ROC from 0.7 to 0.8 indicate reasonable discrimination and values exceeding 0.8 indicate good discrimination. We defined the best cut-off value, as the value with the highest accuracy that maximizes the Youden's index. Youden's index is a single statistic that captures the performance of a dichotomous diagnostic test [28].

Then, within each of the four disease activity categories defined by DAS28-CRP, we analyzed the percentile distributions of RAID. In particular, we focused on the 25th and 75th percentiles mean values for each disease activity status. These values were used to define the RAID thresholds between REM and LDA, LDA and MDA and MDA and HDA. More in detail, the approach was the following: the cut-off between REM and MDA was outlined taking the RAID mean value of the 75th percentile for REM and the RAID mean value of the 25th percentile of MDA. Thereafter, we calculated the arithmetic mean between these two values and the mean smoothed to the nearer whole number. This new value obtained represents the cut-off distinguishing between REM and LDA. With the same methodology, we achieved the cut-off values in the transition from LDA to MDA and from MDA to HDA. We used non-parametric Kruskal-Wallis test to assess the level of significance of different disease activity categories on individual patients. Furthermore, we have created patient groups based on the patients' activity ranks within the cohort and used weighted Kappa statistics to assess the level of overall agreement of different activity categories on individual patients.

The data were analyzed using the SPSS version 11.0 (SPSS Inc, Chicago, IL) and the MedCalc® version 16.0 (MedCalc Software bvba, Ostend, Belgium) for Windows XP.

2.6. Role of the funding source

EULAR had no role in the study design; in the collection, analysis and interpretation of data; in writing the manuscript; and in the decision to submit for publication.

3. Results

In total, 622 RA patients (522 women, 100 men) from 13 European countries (35 patients from Bulgaria, 60 from Croatia, 17 from Estonia, 81 from Italy, 38 from Latvia, 47 from Lithuania, 40 from Poland, 22 from Portugal, 58 from Romania, 61 from Russia, 73 from Serbia, 12 from Slovakia and 78 from Spain) were included in this study from December 2013 to March 2014. Mean age at enrolment was 55 ± 11 years and mean disease duration was 11 ± 9 years. Average CRP level at enrolment was 1.1 ± 1.8 mg/dL. There were 489 (78.6%) RF positive and 392 (63.0%) ACPA positive patients. With regard to treatment, 166 RA patients (27%) were treated with glucocorticoids (prednisone equivalent average dose 5.8 mg/day, max dose 7.5 mg/day). Concerning conventional synthetic DMARDs, 324 RA patients (53%) were receiving methotrexate (average dose 12.5 mg/week), 119 (19%) hydroxychloroquine (average dose 250 mg/day) and 50 (8%) leflunomide (average dose 20 mg/day), finally 9% were treated with biologic agents.

3.1. Central tendency and distributions of RAID questionnaires

Fig. 1 shows the estimate of the central tendency and distributions for RAID. The composite scores of the RAID were not normally distributed (Kolmogorov–Smirnov test) (Fig. 1). Similarly, HAQ-DI and DAS28-CRP showed a non-normal distribution. The RAID median value (95% confidence interval [CI]) was 4.63 (95% CI 3.38 to 4.83). The coefficient of Skewness (degree of symmetry) was

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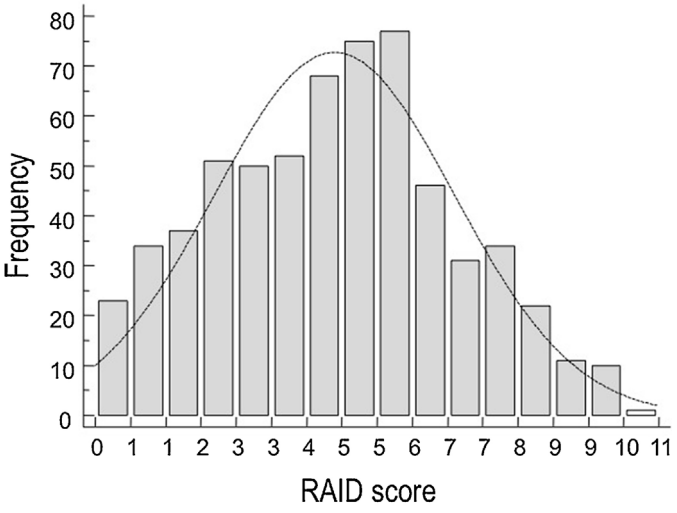

Fig. 1. Histogram with the overall distribution of RAID (622 patients).

0.079 ($P = 0.417$) and coefficient of Kurtosis (degree of peakedness/flatness) –0.5671 ($P = 0.0001$).

Fig. 2 depicts the RAID medians in the different European countries. Higher scores have been founded in patients coming from Estonia (median 6.22), Bulgaria (median 5.28) and Lithuania (median 5.14). Lower values have been recorded in Latvia (median 3.84), Portugal (median 3.93) and Croatia (median 4.03).

3.2. Discriminant validity

The ROC curves to discriminate the ability of RAID, to distinguish patients with active (group A) and non-active disease ("overall" LDA or group B) was very good with an AUC of 0.847 (95% CI: 0.816 to 0.878; $P < 0.0001$). The ROC curve achieved a maximum Youden's index at 4, where sensitivity was 73.5% (95% CI: 68.5 to 77.8) and specificity 86.3% (95% CI: 81.6 to 90.2), with a positive likelihood ratio (LR+) of 5.36 (Fig. 3).

3.3. Convergent validity

There was a high degree of correlation between the RAID with respect to HAQ-DI (rho = 0.651; $P < 0.0001$). Moderate correlations ($P < 0.0001$) were also seen between the RAID questionnaire and the DAS28-CRP (rho = 0.417; $P < 0.0001$). The RAID questionnaire showed also a slight relationship with age (rho = 0.127; $P = 0.035$).

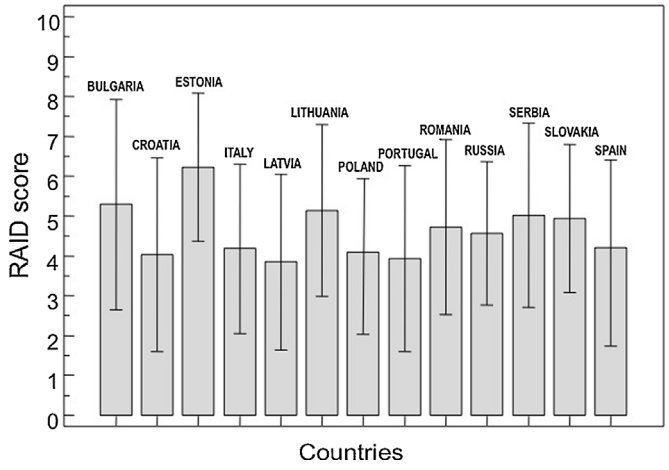

Fig. 2. RAID median values registered in the different European countries.

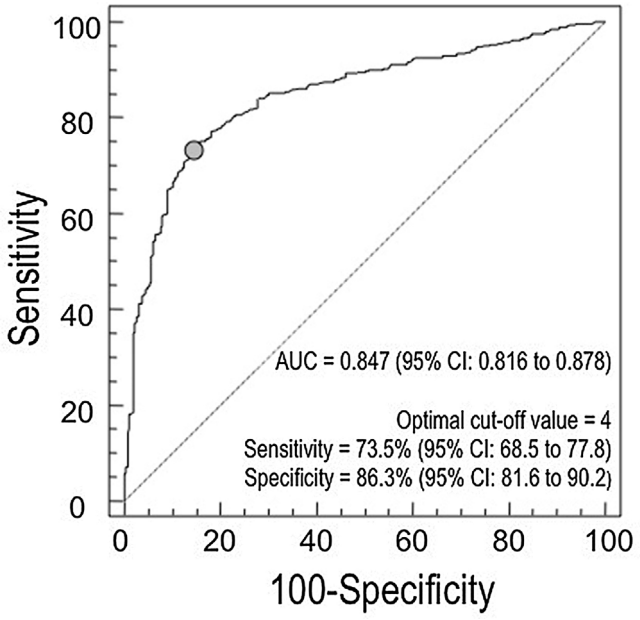

Fig. 3. ROC curve for the performance of RAID in discriminating between patients with active disease (group A) and "overall" LDA (group B). A non-discriminating test has an area of 0.5 and a perfect discriminating test has an area of 1.0. The closer the curve approaches, the upper-left corner of the graph, the more informative the instrument is.

3.4. Definition of disease activity states with RAID

According to the DAS28-CRP classification, 151 patients (24.3%) resulted in REM, 111 patients (17.8%) in LDA, 259 patients (41.6%) in MDA and 101 patients (16.3%) in HDA.

The median values of RAID in each disease activity category were 2.43 for REM, 3.35 for LDA, 4.91 for MDA and 6.66 for HDA (Table 1). The cross-classification showed a significant overall agreement (defined as the percentage of observed exact agreements) (weighted Kappa 0.704 with standard error of 0.038). Table 1 also describes the mean values of the RAID at 25th and 75th percentiles. Applying the approach described above to define

Table 1
Median values, and 25th–75th percentiles distribution of RAID scores for each disease activity category defined by DAS28-CRP.

	Median, 25th and 75th percentiles	95% confidence interval
DAS28-CRP REM (n = 151)		
RAID-median	2.43	2.26–2.63
RAID-25th percentiles	1.64	1.15–1.98
RAID-75th percentiles	3.09	2.93–3.34
DAS28-CRP LDA (n = 111)		
RAID-median	3.35	3.20–3.53
RAID-25th percentiles	2.84	2.43–3.03
RAID-75th percentiles	4.00	3.76–4.25
DAS28-CRP MDA (n = 259)		
RAID-median	4.91	4.64–5.25
RAID-25th percentiles	3.96	3.51–4.21
RAID-75th percentiles	6.32	5.82–6.71
DAS28-CRP HDA (n = 101)		
RAID-Median	6.66	6.15–7.25
RAID-25th percentiles	5.51	4.91–5.97
RAID-75th percentiles	7.80	7.58–8.21

DAS28: 28-joints disease activity score-C-reactive protein; RAID: rheumatoid arthritis impact of disease; REM: remission; LDA: low disease activity; MDA: moderate disease activity; HDA: high disease activity.

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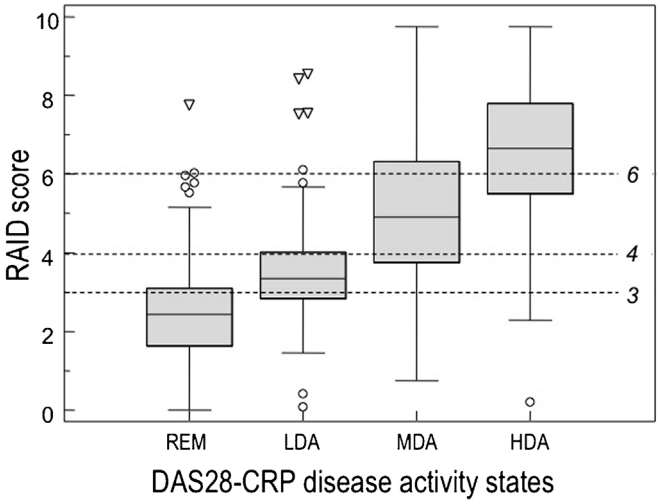

Fig. 4. Box-and-Whisker plots displaying the RAID disease activity states. The boxes represent the RAID values (y-axis) from 25th to 75th percentiles for each disease activity status, as defined by DAS28-CRP (x-axis). The middle lines inside boxes are the medians. The dotted lines are the cut-off values obtained for the transitions between disease activity states (respectively 3, 4 and 6).

the cut-offs in the transition from REM to LDA, the percentiles values considered were 3.09 (RAID mean value at 75th percentile of REM) and 2.84 (RAID mean value at 25th percentile of LDA). The arithmetic mean of these two numbers was 2.96, rounded off to 3, the RAID cut-off for REM. The other RAID cut-off values resulted 4 between LDA and MDA and 6 between MDA and HDA. Fig. 4 shows the RAID disease activity states as defined by DAS28-CRP.

4. Discussion

Incorporation of validated RA disease activity measures into a practice's workflow will facilitate adherence to the ACR/EULAR guidelines for the treatment of RA [3,29]. These RA recommendations include concepts of "treat-to-target" (T2 T) and "tight control". The T2 T approach requires that antirheumatic therapy in a patient should be chosen and adjusted in such a manner that clinical remission or low disease activity is achieved. The "tight control" concept requires frequent assessments of disease activity in order to check the treatment goals and to avoid delays in optimal therapy. It is recommended that monitoring disease activity should be done by composite measures [3,29–32]. A variety of instruments have been described and used for this purpose. Some are purely PROs (RADAI, PAS or PAS-II, RAPID, PRO-CLARA and RAID), some add provider assessment (such as the clinical disease activity index [CDAI]) and some add provider assessment and laboratory acute-phase reactants (such as the simplified disease activity index [SDAI] and DAS28) [33].

In this study, we tried to lay the foundations for a broader application of the RAID in the clinical practice.

Patient-driven composite tools, such as the RAID, have the advantage of being relatively easy to use in clinical practice because they do not require provider assessment, such as the formal joint count. PROs are also correlated with the DAS28 in clinical trials and in clinical settings [10,34]. Patients can often complete these measures on standardized paper or electronic forms in the waiting room, making them very practical to use. A secondary benefit is that PROs based instruments are location-independent and time-independent, offering the opportunity for flexible, patient-tailored, off-site monitoring and management [15,35]. A disease activity measure requires criteria for identifying disease activity states (or status) and a disease activity status portrays the clinical picture in specific timepoints [36].

Compared to the others PROs, before RAID, only the RAPID scores proposed a classification in disease activity categories [9]. The definition of cut-offs is fundamental for a disease activity index, increasing its interpretability and making it more meaningful and likely to be applied both in clinical practice as well as in the research setting [36,37]. The methodology used for RAID cut-offs determination of disease activity states (25th and 75th percentiles mean values) is a valid approach, already employed in the rheumatology scientific literature [37,38]. Thus, based on the distributions of RAID in the different disease activity states, as defined by DAS28-CRP, we propose cut-off values for REM (RAID ≤ 3), for LDA (RAID >3 and ≤ 4), for MDA (RAID >4 and ≤ 6) and for HDA (RAID >6) (Fig. 4). Mean RAID differed significantly between patients classified as REM, LDA, MDA or HDA ($P<0.001$). Furthermore, a second alternative method commonly used for establishing "optimal" cut-points [36,37], such as the point on the ROC curve closest to (0, 1) (Youden's index), confirmed the value of 4 in the distinction from active to non-active disease (with a LR+of 5.36).

The results displayed in this paper appear as reliable thresholds for defining activity and we think that could be used for designing future clinical trials. Dougados et al. suggested how to interpret the RAID scores in terms of MCII and PASS [18] and a successive research confirmed that patients who considered their state satisfactory rated their RAID score of 2.1 [39]. However, a formal definition of disease activity was not available for this index. The addition of disease activity states cut-offs, proposed in this paper, to the existing features of the instrument already explored (MCII and PASS), and increases the clinimetric properties of this tool.

This study has weaknesses and strengths. A weakness may be the lack of a universal and broadly accepted "gold standard" for clinical disease activity in RA. In our cohort, information about CDAI or SDAI, nowadays widely considered the principal tools to assess disease activity were not available. However, we believe that the use of DAS28 EULAR criteria as external constructs and their remarkable consistence for the selection of cut-offs overcomes these limitations. Further, this was a post-hoc analysis and not a longitudinal study. The lack of longitudinal data does not allow to evaluate the responsiveness of the RAID cut-off values proposed. Our cross-sectional cohort is, however, adapted to the present objectives.

The major strengths of this study are related to the sample size and to the cohort composition. Patients were coming from several countries, with a variety of cultures and socioeconomic backgrounds and with different disease activity gathered from daily practice not in a trial setting. Thus, we believe that the study population may be well representative of patients with RA followed in tertiary care centers in Europe. Furthermore, the disease burden in RA extends beyond the joint. Physical and psychosocial extra-articular burden of treated RA patients and relationships among diverse disease manifestations need to be considered [40].

In summary, the RAID constitutes a validated and feasible tool for RA disease activity assessment. The incorporation of this measure into a practice's workflow will facilitate adherence to the ACR/EULAR guidelines for the treatment of RA and provide a useful instrument for tight control strategies.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgements

This study was supported by EULAR in the context of a broader cross-sectional study (project No. CLI064) for the development and

validation of a patient-reported outcome questionnaire to estimate vitamin D status (D-PRO).

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Please cite this article in press as: Salaffi F, et al. Validity of the rheumatoid arthritis impact of disease (RAID) score and definition of cut-off points for disease activity states in a population-based European cohort of patients with rheumatoid arthritis. Joint Bone Spine (2017), http://dx.doi.org/10.1016/j.jbspin.2017.05.020