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# Remission, Minimal Disease Activity, and Acceptable Symptom State in Juvenile Idiopathic Arthritis

## Defining Criteria Based on the Juvenile Arthritis Disease Activity Score

Alessandro Consolaro,[1] Giulia Bracciolini,[1] Nicolino Ruperto,[1] Angela Pistorio,[1] Silvia Magni-Manzoni,[2] Clara Malattia,[1] Silvia Pederzoli,[1] Sergio Davì,[1] Alberto Martini,[3] and Angelo Ravelli[3], for the Paediatric Rheumatology International Trials Organization

***Objective.*** **To determine cutoff values for defining remission, minimal disease activity, and parent and child acceptable symptom state in juvenile idiopathic arthritis (JIA) using the Juvenile Arthritis Disease Activity Score (JADAS).**

***Methods.*** **For the selection of cutoff values, data from a clinical database including 609 children with JIA were used. Optimal cutoff values were determined against external criteria by calculating the 75th percentile of cumulative score distribution and through receiver operating characteristic curve analysis. External criteria included formal definitions of inactive disease and minimal disease activity, subjective rating of remission by physicians, parents, and children, and rating of acceptable symptom state by parents and children. The choice of cutoffs was made based on clinical and statistical grounds. Cross-validation was performed using 4 JIA patient samples that included a total of 1,323 patients, and was based on assessment of construct, discriminant, and predictive validity.**

***Results.*** **With all versions of the JADAS, the cutoff score for classifying a patient as having inactive disease was 1, whereas the cutoff for classification of minimal disease activity was 2 for oligoarticular JIA and 3.8 for polyarticular JIA. Cutoffs for physicians', parents', and children's subjective rating of remission ranged from 2 to 2.3. Cutoffs for acceptable symptom state ranged from 3.2 to 5.4 for parents and from 3 to 4.5 for children. Results of cross-validation analyses strongly supported the selected cutoff values.**

***Conclusion.*** **Cutoff values for classifying various disease states in JIA using the JADAS were developed. In cross-validation analyses, they proved to have good construct and discriminant validity and ability to predict disease outcome.**

In the last decade there has been major progress in the management of juvenile idiopathic arthritis (JIA), which includes the shift toward early aggressive intervention and the development of new therapeutic agents and combination treatment strategies (1–5). These advances have increased the potential for achievement of disease remission or, at least, low levels of disease activity, and have consequently moved the therapeutic aims increasingly toward attainment of inactive disease status (6–11). For reliable documentation of the advances in therapeutic efficacy, there is a need for validated and clinically useful criteria that describe precisely the clinical states of remission or near-remission.

One approach to defining remission is based on the use of a core set of multiple criteria, such as those included in Wallace and colleagues' preliminary definitions of inactive disease and clinical remission in JIA (6). Based on these criteria, a patient is classified as having inactive disease at a specific point in time when he/she has no joints with active disease, no systemic manifestations attributable to JIA, no active uveitis, normal levels of acute-phase reactants, and a physician's global assess-

[1]Alessandro Consolaro, MD, Giulia Bracciolini, MD, Nicolino Ruperto, MD, MPH, Angela Pistorio, MD, PhD, Clara Malattia, MD, PhD, Silvia Pederzoli, MD, Sergio Davì, MD: Istituto G. Gaslini, Genoa, Italy; [2]Silvia Magni-Manzoni, MD: Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy; [3]Alberto Martini, MD, Angelo Ravelli, MD: Istituto G. Gaslini and Università degli Studi di Genova, Genoa, Italy.

Address correspondence to Angelo Ravelli, MD, Pediatria II, Istituto G. Gaslini, Largo G. Gaslini 5, 16147 Genoa, Italy. E-mail: angeloravelli@ospedale-gaslini.ge.it.

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ment of disease activity indicating no disease activity. However, achievement of a complete absence of any measurable sign of disease activity is infrequent in the short time frame of a clinical trial and is still problematic in clinical practice in many children with JIA, particularly among those with polyarticular or systemic disease. This has highlighted the need for establishing a well-defined state of minimal disease activity as an intermediate state between high disease activity and remission, though very close to remission (9).

It has been argued that the criteria for inactive disease (6) are insufficient in that they are based only on physician-reported outcomes and an acute-phase reactant level, whereas parent proxy–reported and child self-reported outcomes are neglected (8). Although parent global assessment is part of the criteria for minimal disease activity in polyarthritis, no parent/child-reported measures are included in the definition of minimal disease activity in oligoarthritis. Hence, definitions of both inactive disease and minimal disease activity may not adequately reflect the parent's and child's perception of the disease status. The need to know whether a therapeutic intervention leads to an acceptable state according to the parent or the child has led us to propose the concept of parent/child acceptable symptom state (12).

An alternative approach to the measurement of disease activity is based on composite disease activity scores. These tools are designed to quantify the absolute level of disease activity by providing one summary number on a continuous scale. Recently, a composite disease activity score for JIA, the Juvenile Arthritis Disease Activity Score (JADAS), was developed; in validation analyses it was found to have good metrologic properties, including the ability to predict disease outcome (13).

To aid in interpretation of scores on the JADAS, criteria (i.e., cutoff values) are needed for identifying high and low levels of JIA activity. These criteria may provide simple and intuitive reference values that can be used to monitor the disease course over time in an individual patient or to compare disease status across individual patients or patient groups. Furthermore, they may support decisions about enrollment into clinical trials as well as requirements for changes in therapies and for defining therapeutic goals. This study was undertaken to determine and validate cutoff values in the JADAS that correspond to the states of inactive disease and minimal disease activity or reflect the physician's, parent's, or child's subjective rating of remission or the parent's or child's satisfaction with the outcome of the illness.

## PATIENTS AND METHODS

**JADAS calculation.** The JADAS is computed by assessing the following variables: 1) physician global rating of overall disease activity, measured on a 10-cm horizontal visual analog scale (VAS) or a 21-numbered circle VAS (14) (0 = no activity; 10 = maximum activity for both VAS); 2) parent/child ratings of well-being and pain, assessed on a 10-cm horizontal VAS or a 21-numbered circle VAS (14) (0 = best; 10 = worst for both VAS); 3) number of active joints, assessed in 71, 27, or 10 joints (JADAS71, JADAS27, and JADAS10, respectively); and 4) Westergren erythrocyte sedimentation rate (ESR), normalized to a 0–10 scale. The JADAS is calculated as the sum of the scores of its 4 components, which yields a global score of 0–101, 0–57, and 0–40 for the JADAS-71, JADAS-27, and JADAS-10, respectively (13).

**Study population used for selection of cutoff values, and nomenclature of disease states.** The present study was approved by the Istituto G. Gaslini Institutional Review Board. For the selection of JADAS cutoff values in this study, we used data from a clinical database including 609 children who met the International League of Associations for Rheumatology (ILAR) criteria for JIA (15) and had undergone a total of 1,814 visits at study centers between March 2007 and December 2009. Forty-six patients had systemic arthritis, 267 had persistent oligoarthritis, 96 had extended oligoarthritis, 138 had rheumatoid factor (RF)–negative polyarthritis, 9 had RF-positive polyarthritis, 15 had psoriatic arthritis, 13 had enthesitis-related arthritis, and 25 had undifferentiated arthritis. Other clinical features of these patients have been described previously (16). Because inactive disease, minimal disease activity, or a satisfactory disease state is more likely to be achieved in the later stages of followup, data from each patient's last visit were used for the present analyses. Child-reported outcomes were included in the analyses whenever available.

All visits were reviewed to identify those in which the patient met the preliminary criteria for inactive disease or minimal disease activity in JIA. The state of inactive disease was defined as described above. The state of minimal disease activity was defined as the presence of all of the following: physician's global assessment of disease activity of $\leq$3.5, parent's global rating of well-being of $\leq$2.5, and swollen joint count of $\leq$1 in patients with polyarthritis, and physician's global assessment of disease activity of $\leq$2.5 and swollen joint count of 0 in patients with oligoarthritis. This definition was developed and validated recently (9). Children with systemic arthritis, RF-positive polyarthritis, RF-negative polyarthritis, or extended oligoarthritis were included in the polyarthritis group. The oligoarthritis group included children with persistent oligoarthritis. Children with JIA that was classified in the remaining ILAR categories were assigned to the polyarthritis or oligoarthritis group based on the number of joints affected during the disease course ($>$4 or $\leq$4, respectively).

During the study period, all parents and children (if age $\geq$7–8 years) seen at the study center were asked at each visit to independently complete a multidimensional question-

naire, the Juvenile Arthritis Multidimensional Assessment Report (16), that included a subjective rating of the child's disease state as remission, continued activity, or relapse, defined as previously reported (12), and a question about satisfaction with the current outcome of the illness. The question on perceived satisfactory health state for parents (children) was, "Considering all the ways the illness affects your child (you), would you be satisfied if his/her (your) condition remained stable/unchanged for the next few months?" (12,17). The response options were "yes" or "no." At the same visit, the attending physician was asked to subjectively and independently rate the child's disease state as remission, continued activity, or relapse.

By definition, no child with inactive disease had active uveitis, whereas this complication was present in 6–8 children (depending on the definition used) who had minimal disease activity or whose disease was rated subjectively as being in remission by the physician, the parent, or the child or was judged as being in an acceptable symptom state by the parent or the child. No child in any of the above categories had active systemic manifestations, and only 1 child had active psoriatic lesions.

**Study populations used for cross-validation of the cutoff values.** Four JIA patient samples were used to cross-validate the selected cutoff values. The first sample was composed of 595 patients with polyarthritis enrolled in a controlled trial conducted by the Pediatric Rheumatology International Trials Organization, comparing intermediate versus higher doses of methotrexate (MTX) (18). For the present analysis, the baseline and 6-month visits of the initial screening phase of the trial were used. The second was a cross-sectional sample of 310 patients with disease duration of $\geq$5 years who were included in a long-term outcome survey (19). The third sample included 358 unselected patients with 2 or more visits to the authors' clinics between January 1997 and December 2002. For the purpose of the analysis, data from the first visit and the last followup visit, made after a median of 1.7 years (range 0.7–3 years), were used. The fourth sample consisted of 60 of the 103 patients included in a recent study on the validation of versions of the Sharp/van der Heijde score (SHS) adapted for children (20), in whom the SHS had been determined at first observation and after 3 years and sufficient clinical data were available.

**Statistical analyses used for selection of the cutoff values.** Optimal cutoff values were determined against external criteria (i.e., the various disease states, as defined above) by calculating the 75th percentile (upper quartile) of cumulative score distribution and through receiver operating characteristic (ROC) analysis. In the ROC analysis, 3 different methods were applied: 1) the closest point to (0,1), i.e., the point where the shoulder of the ROC curve is closest to the left upper corner of the graphic; 2) the Youden index (21); and 3) fixed 90% specificity. The upper quartile is an intuitive and straightforward midpoint between the median of the category and its maximum (which would reflect 100% sensitivity regardless of the degree of specificity) and is a robust measure (22). The first and second methods of ROC analysis provide the best balance between sensitivity and specificity. The fixed 90% specificity method was considered to be powerful enough to minimize the rate of misclassification of patients with moderate/high disease activity as having inactive disease (23,24).

**Cross-validation study.** Cross-validation of the cutoff values was based on assessment of construct, discriminant, and predictive validity. These were assessed using various approaches as described below.

*Calculation of the percentage of patients who had a JADAS below the cutoff value for each disease state at 6 months in the MTX trial, in relation to level of improvement according to the American College of Rheumatology (ACR) criteria (25).* Patients from the MTX trial (18) were divided into 4 mutually exclusive groups (nonresponders, ACR Pediatric 30 [Pedi 30] responders, ACR Pedi 50 responders, and ACR Pedi 70 responders) according to their maximum level of improvement at 6 months. It was predicted that a proportionally greater percentage of patients with a JADAS below each cutoff value would correspond with nonresponse and ACR Pedi 30, Pedi 50, and Pedi 70 response levels (e.g., the greater the ACR Pedi response the more patients with a JADAS below the cutoff value).

*Calculation of the percentage of patients in the sample with longstanding disease who had a JADAS below the cutoff value for each disease state, in relation to disability and quality of life parameters.* In patients from the sample with a JIA duration of $\geq$5 years (19), JADAS at the cross-sectional visit was calculated. The proportion with a JADAS below the cutoff value for each disease state category assessed was then investigated in relation to 1) the absence or presence of physical disability, defined as a Childhood Health Assessment Questionnaire (C-HAQ) score (26) of 0 or $>$0, respectively, or a Steinbrocker functional classification (27) of 1 or $>$1, respectively; 2) the absence or presence of articular damage, defined as a Juvenile Arthritis Damage Index articular score (28) of 0 or $>$0, respectively; 3) the absence or presence of radiographic joint damage, defined as a Poznanski score (29) of $\geq -2$ units or $< -2$ units, respectively; and 4) normal or impaired health-related quality of life (HRQOL), defined as a Child Health Questionnaire physical summary score or psychosocial summary score (30) of $\geq$40 or $<$40, respectively. It was predicted that, for each disease state category assessed with the JADAS, the proportion of patients with a JADAS below the cutoff value would be greater among patients with absence of physical disability or articular damage, or normal HRQOL.

*Assessment of the ability of the JADAS cutoff values to predict inactive disease.* The third patient sample (unselected patients attending the authors' clinics) was used in the analysis of the ability of the JADAS cutoff values to predict inactive disease in JIA. We calculated whether the patients did or did not have a JADAS below the cutoff value for each disease state at the first visit, and determined whether they met the definition of inactive disease (6) at the last followup visit. It was predicted that the proportion of patients who had a JADAS below the cutoff at the first visit would be greater among patients with inactive disease at the final visit.

*Assessment of the ability of the JADAS cutoff values to predict achievement of normal functional status.* The third patient sample was also used in the analysis of the ability of the JADAS cutoff values to predict achievement of normal functional status. We calculated whether the patients did or did not have a JADAS below the cutoff value for each disease state at the first visit, and related this to the C-HAQ score at the last

**Table 1.** JADAS27 cutoff values for classification of patients into various JIA disease states according to 4 different methods for determining optimal cutoffs*

| Disease state | n (P + N) | Method for determination of optimal cutoff† | | | | AUC (95% CI) |
|---|---|---|---|---|---|---|
| | | 75th percentile | Youden | (0,1) | 90% specificity | |
| Inactive disease | 480 (175 + 305) | 1 (83.4/88.2)‡ | 1 (83.4/88.2)‡ | 1 (83.4/88.2)‡ | 1 (83.4/88.2)‡ | 0.93 (0.90–0.95) |
| Physician-assessed remission | 456 (239 + 217) | 2 (82.8/94.5)‡ | 2.5 (87.4/90.8) | 2.5 (87.4/90.8) | 2.5 (87.4/90.8) | 0.95 (0.93–0.97) |
| Parent-assessed remission | 462 (244 + 218) | 2 (77.9/89.9) | 2.3 (78.7/89.9)‡ | 2.3 (78.7/89.9)‡ | 2.3 (78.7/89.9)‡ | 0.92 (0.89–0.95) |
| Child-assessed remission | 263 (150 + 113) | 2 (78/87.6) | 2.2 (80/87.6)‡ | 2.2 (80/87.6)‡ | 2 (78/87.6) | 0.92 (0.88–0.95) |
| Minimal disease activity, oligoarthritis | 239 (135 + 104) | 2 (80.7/87.5)‡ | 2.5 (87.4/85.6) | 2.5 (87.4/85.6) | 1.8 (71.1/91.3) | 0.94 (0.89–0.96) |
| Minimal disease activity, polyarthritis | 239 (115 + 124) | 1.6 (73.9/97.6) | 3.8 (96.5/91.3)‡ | 3.8 (96.5/91.3)‡ | 4 (97.4/88.9) | 0.98 (0.96–0.99) |
| Parent acceptable symptom state | 474 (348 + 126) | 4.5 (73.6/90.5) | 4.7 (77.6/90.5)‡ | 4.7 (77.6/90.5)‡ | 4.9 (77.6/89.7) | 0.91 (0.88–0.93) |
| Child acceptable symptom state | 273 (182 + 91) | 4 (79.1/75.2)‡ | 3.1 (74.2/83.2) | 3.1 (74.2/83.2) | 2 (67.6/87.6) | 0.86 (0.82–0.90) |

* JADAS27 = 27-joint Juvenile Arthritis Disease Activity Score; JIA = juvenile idiopathic arthritis; P + N = number of positive + negative results according to external criteria for the disease state; AUC = area under the curve; 95% CI = 95% confidence interval.
† Values are the cutoff (sensitivity/specificity). 75th percentile = cutoff according to the 75th percentile of the cumulative score distribution; (0,1) = cutoff according to the closest point to (0,1); Youden = cutoff according to the Youden index; 90% specificity = cutoff according to fixed 90% specificity (see Patients and Methods for details).
‡ Chosen cutoff value.

followup visit. It was predicted that the proportion of patients who had a JADAS below the cutoff at the first visit would be greater among patients with a C-HAQ score of 0 at the final visit.

*Assessment of the ability of the JADAS cutoff values to predict progression of radiographic joint damage.* In patients from the study of adapted versions of the SHS for children (20), the SHS at 3 years was compared between patients who had and those who had not reached a JADAS below the cutoff value for each disease state during the 3 years of observation. It was predicted that the SHS at 3 years would reflect less impairment in patients who had a JADAS below the cutoff at 1 or more visits than in patients who had never reached a JADAS below the cutoff.

For each outcome assessed, the prediction was considered as met when the difference in percentages was statistically significant. Quantitative data were compared by Mann-Whitney U test. Percentage data were compared by chi-square test. All statistical tests were 2-sided, and *P* values less than 0.05 were considered significant. The statistical packages used were Statistica (StatSoft) and Stata, version 7 (StataCorp).

## RESULTS

**Selection of the optimal cutoff values for classification of specific disease states.** The cutoff values obtained for the JADAS27 according to the various external criteria are presented in Table 1. The cutoffs obtained for the JADAS71 and the JADAS10 were very similar to those obtained for the JADAS27. As expected, the cutoff values for classification of a patient as meeting criteria for inactive disease, which are the most stringent, were the lowest. All cutoff values yielded by physicians', parents', and children's subjective ratings of remission were between 2 and 3. The cutoffs for minimal disease activity in polyarthritis were higher than those for minimal disease activity in oligoarthritis, and the cutoffs for the acceptable symptom state were lower for the children's ratings than for the parents'.

The following criteria were used to select the final cutoffs. The 90% specificity criterion was considered to be the most clinically relevant method to identify the cutoffs for the different states, in order to separate them most efficiently from high disease states. Specificity was considered more important than sensitivity in order to reduce the risk of misclassifying patients whose disease was actually active. However, a minimum sensi-

**Table 2.** Proposed JADAS cutoff values for each JIA disease state*

| Disease state | All JIA | Oligoarthritis | Polyarthritis |
|---|---|---|---|
| Inactive disease | 1 | 1 | 1 |
| Physician-assessed remission | 2 | 2 | 2 |
| Parent-assessed remission | 2.3 | 2.3 | 2.3 |
| Child-assessed remission | 2.2 | 2.2 | 2.2 |
| Minimal disease activity | – | 2 | 3.8 |
| Parent acceptable symptom state | 4.7 | 3.2/3.5† | 5.2/5.4† |
| Child acceptable symptom state | 4 | 3 | 4.3/4.5† |

* Cutoff values apply to all versions of the Juvenile Arthritis Disease Activity Score (JADAS) (i.e., the 27-joint JADAS [JADAS27], the 10-joint JADAS [JADAS10], and the 71-joint JADAS [JADAS71]) unless otherwise indicated. JIA = juvenile idiopathic arthritis.
† Cutoff value for the JADAS27/cutoff value for the JADAS10 and JADAS71.

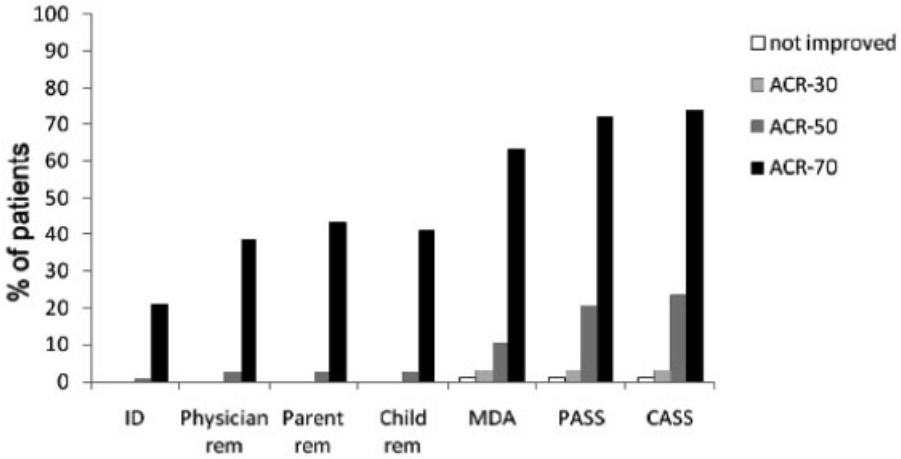


**Figure 1.** Percentage of patients with a 27-joint Juvenile Arthritis Disease Activity Score below the cutoff values for various disease states according to response at 6 months in the methotrexate trial as assessed by American College of Rheumatology (ACR) Pediatric criteria (not improved, or improved by 30%, 50%, or 70% [ACR 30, ACR 50, and ACR 70, respectively]). $P < 0.0001$ for all comparisons of ACR 70 responders versus other response groups. ID = inactive disease; rem = remission (assessed by the physician, the parent, or the child); MDA = minimal disease activity; PASS = parent acceptable symptom state; CASS = child acceptable symptom state.

tivity of 75% was needed to ensure adequate face validity of the criteria. Among the cutoffs yielded by the different methods, those with a minimum specificity of 90% and a minimum sensitivity of 75% were therefore retained. If more than one cutoff met this requirement, the value with the highest specificity was selected. If more than one value had the same specificity, the value with the highest sensitivity was chosen. If none of the cutoffs for a particular disease met the above requirement, the cutoff with a minimum sensitivity of 75% and the highest specificity was selected. The final JADAS cutoff values for the various disease states proposed for JIA as a whole and for the oligoarthritis and polyarthritis subsets considered separately are shown in Table 2.

**Results of cross-validation analyses.** The percentage of patients who had a JADAS below the cutoff value for each disease state at 6 months in the MTX trial sample in relation to the level of ACR Pedi response is presented in Figure 1. The proportion of patients with a JADAS value below the cutoffs was greatest among those with improvement at the ACR Pedi 70 level. The percentage of ACR Pedi 50 responders who met the JADAS cutoffs was much lower, although it increased progressively from inactive disease to physician's, parents', and children's subjective remission ratings, to minimal disease activity, to acceptable symptom state. A negligible percentage of ACR Pedi 30 responders and nonresponders met the JADAS cutoffs.

**Table 3.** Percentage of JIA patients in whom inactive disease had been achieved at the final visit, according to the JADAS71 value (below the cutoff or above the cutoff) for each disease state at the first visit*

| Disease state | JADAS71 below cutoff at first visit | JADAS71 above cutoff at first visit | *P* |
|---|---|---|---|
| Inactive disease | 31/74 (41.9) | 81/284 (28.5) | 0.03 |
| Physician-assessed remission | 43/93 (46.2) | 69/265 (26.0) | 0.0003 |
| Parent-assessed remission | 43/96 (44.8) | 69/262 (26.3) | 0.0008 |
| Child-assessed remission | 43/95 (45.3) | 69/263 (26.2) | 0.0006 |
| Minimal disease activity, oligoarthritis | 30/64 (46.9) | 39/131 (29.8) | 0.02 |
| Minimal disease activity, polyarthritis | 20/45 (44.4) | 23/118 (19.5) | 0.001 |
| Parent acceptable symptom state | 55/132 (41.7) | 57/226 (25.2) | 0.001 |
| Child acceptable symptom state | 54/124 (43.5) | 58/234 (24.8) | 0.0003 |

* Values are the number with inactive disease at the final visit/number assessed (%). JIA = juvenile idiopathic arthritis; JADAS71 = 71-joint Juvenile Arthritis Disease Activity Score.

**Table 4.** Percentage of JIA patients with a C-HAQ score of 0 at the final visit, according to the JADAS71 value (below the cutoff or above the cutoff) for each disease state at the first visit*

| Disease state | JADAS71 below cutoff at first visit | JADAS71 above cutoff at first visit | *P* |
|---|---|---|---|
| Inactive disease | 59/74 (79.7) | 153/284 (53.9) | <0.0001 |
| Physician-assessed remission | 75/93 (80.6) | 137/265 (51.7) | <0.0001 |
| Parent-assessed remission | 78/96 (81.3) | 134/262 (51.1) | <0.0001 |
| Child-assessed remission | 77/95 (81.1) | 135/263 (51.3) | <0.0001 |
| Minimal disease activity, oligoarthritis | 52/64 (81.3) | 77/131 (58.8) | 0.002 |
| Minimal disease activity, polyarthritis | 35/45 (77.8) | 48/118 (40.7) | <0.0001 |
| Parent acceptable symptom state | 103/132 (78.0) | 109/226 (48.2) | <0.0001 |
| Child acceptable symptom state | 97/124 (78.2) | 115/234 (49.1) | <0.0001 |

* Values are the number with a Child Health Assessment Questionnaire (C-HAQ) score of 0 at the final visit/number assessed (%). JIA = juvenile idiopathic arthritis; JADAS71 = 71-joint Juvenile Arthritis Disease Activity Score.

Also as predicted, the percentage of patients who had a JADAS value below the cutoffs at ≥5 years after disease onset was greater among those who had normal physical function than among those who had impaired physical function. Similar findings were observed when patients were compared for the absence or presence of clinical or radiographic joint damage, or the presence of normal or impaired HRQOL in the physical or (to a lesser extent) psychosocial domain (data available at http://www.printo.it/articleImage.asp).

In the third patient sample, the percentage of patients with inactive disease or with a C-HAQ score of 0 at the final visit was greater among patients who had a JADAS below the cutoff value at the first visit than among those who did not (Tables 3 and 4). Furthermore, in the fourth patient sample the change in the SHS from baseline to 3 years was lower among patients who had achieved a JADAS below the cutoffs at least once during the 3 years of observation than in those who had not (Table 5). These findings indicated that disease outcome could be predicted using the JADAS cutoff values we developed.

## DISCUSSION

In this study we sought to determine the cutoff values on the JADAS scales that corresponded with meeting criteria for inactive disease (6) or minimal disease activity (9), or reflected the physician's, parent's, and child's subjective rating of remission or the parent's and child's satisfaction with illness outcome. The cutoff values were developed using a routine care population and were cross-validated in 4 data sets, comprising a total of 1,323 patients included in a clinical trial or in a long-term outcome survey, or followed up during standard clinical care.

The finding that the cutoff values obtained for inactive disease were the lowest was expected, as the definition of this disease state is very stringent. Meeting the current criteria for inactive disease requires that 3 of the 4 items of the JADAS (physician global assessment, active joint count, and ESR) are scored as 0. However, the cutoff values obtained for inactive disease were consistently ≥1. This is due to the parent global assessment (which is the fourth component of the JADAS, but

**Table 5.** Change in the SHS in JIA patients from baseline to the 3-year visit, according to whether a JADAS71 value below the cutoff had been achieved at any visit during the 3-year observation period*

| Disease state | JADAS71 below cutoff at ≥1 visit | JADAS71 above cutoff at all visits | *P* |
|---|---|---|---|
| Inactive disease | 1.3 (0, 6) (n = 22) | 7.8 (1, 20) (n = 38) | 0.05 |
| Physician-assessed remission | 1 (−0.3, 5.3) (n = 24) | 8.3 (1, 25) (n = 36) | 0.008 |
| Parent-assessed remission | 1 (0, 6) (n = 25) | 8.5 (1, 30) (n = 35) | 0.009 |
| Child-assessed remission | 1 (0, 6) (n = 25) | 8.5 (1, 30) (n = 35) | 0.009 |
| Minimal disease activity, polyarthritis | 1 (0, 6) (n = 31) | 15.5 (5, 31) (n = 29) | 0.0002 |
| Parent acceptable symptom state | 1 (0, 6) (n = 37) | 16 (7.5, 32.5) (n = 23) | 0.00009 |
| Child acceptable symptom state | 1 (0, 6) (n = 31) | 15.5 (5, 31) (n = 29) | 0.0002 |

* Values are the median (interquartile range) change in the Sharp/van der Heijde score (SHS). JIA = juvenile idiopathic arthritis; JADAS71 = 71-joint Juvenile Arthritis Disease Activity Score.

is not incorporated in the inactive disease criteria) not always being 0 when the score of the other 3 items was 0. We previously found that in 65 of 265 visits (24.5%) in which the physician and/or the parent rated the global score as 0 on a VAS, the parent did not provide a global score of 0 when the physician did (31). Taken together, these observations suggest that the criteria for inactive disease would need to be revised should the parents' or children's evaluation of disease remission be incorporated. Recently, the criteria were modified by adding duration of morning stiffness of ≤15 minutes (32). However, this assessment is not sufficient to capture parents' and children's perception of the burden of disease activity.

Clearly, when remission is interpreted as the total absence of signs and symptoms of disease activity, the use of criteria for inactive disease is most appropriate. However, achievement of true inactive disease either in routine practice or in clinical trials is still problematic in many patients, particularly those with polyarticular or systemic JIA. Furthermore, the state of inactive disease is often not maintained over long periods (7). It has been suggested that in standard clinical care a more attainable goal could be to induce and maintain at least a state of minimal disease activity, which is an intermediate state between high disease activity and remission, though very close to remission (9). In accordance with this definition, the cutoff values that corresponded to fulfilling criteria for minimal disease activity in the present study were slightly higher than those for inactive disease.

To investigate whether and to what extent the formal definitions of inactive disease and minimal disease activity paralleled the physician's, parent's, and child's subjective perception of the state of disease remission, we computed the JADAS cutoff values that corresponded with a disease state categorized subjectively and independently as remission by each of these 3 groups of raters. The cutoff values for remission as rated by physicians, parents, and children were remarkably similar, which suggests that the use of a composite score such as the JADAS, which includes both physician-centered and parent/child-centered outcome measures, may lead to concordant estimates. Overall, the cutoff values obtained for subjective assessment of remission were close to those for minimal disease activity in oligoarthritis, whereas they were approximately midway between those for inactive disease and for minimal disease activity in polyarthritis. The finding that the cutoff values for subjectively defined remission did not overlap with those for inactive disease indicates that physicians, parents, and children may judge the disease as being in remission in the presence of some signs, albeit minimal, of disease activity.

The cutoff values corresponding to a disease state considered acceptable by parents and children were the highest, which suggests that parents and children do not require strict remission to feel satisfied and may consider a level of disease activity that is a bit higher than minimal disease activity to be acceptable. As found previously (12), the cutoff values were lower as judged by children than by parents, which means that children may require better control of disease activity to declare themselves as satisfied.

In cross-validation analyses, all cutoff values revealed a strong ability to discriminate between different levels of ACR Pedi response in a clinical trial. Importantly, the cutoff values for inactive disease, minimal disease activity, and subjectively defined remission were reached in a sizable proportion of cases only by ACR Pedi 70 responders, implying that only an improvement in symptoms of at least 70% makes a substantial difference in disease status in patients with JIA. The achievement of an ACR Pedi 70 response at 6 months after the start of MTX therapy was previously found to predict more favorable long-term outcome (including the presence of inactive disease) in patients with JIA (33).

There is little information on the impact of reaching a state of inactive disease or minimal disease activity on physical function, structural joint damage, and HRQOL as these outcomes are not incorporated in the criteria for either of these disease states. In a long-term outcome study, we found that the proportion of JIA patients with JADAS values below the cutoffs at ≥5 years after disease onset was greater among those with normal physical function, no joint damage, and better-preserved HRQOL (19). This is consistent with the observation that achievement of a state of remission or near-remission may prevent functional impairment and structural joint deterioration (34) and help in maintenance of a satisfactory HRQOL. The finding that patients with normal physical well-being were more likely to meet the cutoff values than patients with normal psychosocial well-being is consistent with the notion that psychosocial health is affected by many factors other than disease activity (35,36). Further evidence of the prognostic validity of the cutoff values was provided by the finding that their achievement was associated with a greater likelihood of having inactive disease or a C-HAQ score of 0 at last followup visit and with less long-term progression of radiographic joint damage.

Overall, the cutoff values yielded with the 3 versions of the JADAS were very similar. In the clinical

setting, the JADAS27 may be preferable over the JADAS71 as evaluation of 27 joints is more feasible and less tedious than evaluation of 71 joints. The JADAS10 is the simplest version, with a 10-joint reduced count. However, it does not enable precise assessment of joint disease, which may limit the ability to detect new joint involvement over time.

Several potential limitations should be taken into account when interpreting our results. Physicians were asked to provide their rating of remission on the basis of a subjective impression and not through evaluation of clinical profiles. Furthermore, treatment decisions were not used as criteria. However, subjective ratings recorded during patient visits have the advantage of reflecting the real world of clinical practice. In addition, visits included in the study likely covered the entire spectrum of therapeutic interventions used in JIA. Cutoff values specific for systemic arthritis, enthesitis-related arthritis, or psoriatic arthritis could not be developed, owing to the insufficient number of study patients in these JIA subsets. We recognize that the decision to aggregate patients with JIA in different ILAR categories based on the number of affected joints is arbitrary and may have affected the reliability of the results. Another potential caveat in our analysis is that clinical perceptions vary between physicians from different regions. Likewise, parents' and children's perceptions of disease activity and burden may vary across ethnic and cultural environments. Thus, the cutoff values need to be tested in different geographic areas and clinical settings before they can be put into widespread use. Finally, we acknowledge that we did not address "biologic remission," i.e., remission defined using imaging studies or biomarkers, and that the concept of "drug-free remission" was not implied by the term "remission" used in our study.

In summary, we have developed JADAS cutoff levels for classification of various disease states in JIA. The cutoffs exhibited good metrologic properties and proved able to predict disease outcome. Based on these good measurement characteristics, they are potentially applicable in clinical practice, observational studies, and clinical trials. However, we do not believe the cutoffs should be used to "diagnose" remission. Rather, they represent an additional clinical tool that, if applied regularly in daily practice, may allow tighter therapeutic control of disease, support the optimization of treatment on an individual patient basis, and help prevent the development of joint damage and physical disability.

## AUTHOR CONTRIBUTIONS

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

**Study conception and design.** Consolaro, Ruperto, Martini, Ravelli.

**Acquisition of data.** Consolaro, Bracciolini, Magni-Manzoni, Malattia, Pederzoli, Davì.

**Analysis and interpretation of data.** Consolaro, Ruperto, Pistorio, Martini, Ravelli.

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