

Definition and Validation of the American College of Rheumatology 2021 Juvenile Arthritis Disease Activity Score Cutoffs for Disease Activity States in Juvenile Idiopathic Arthritis

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This work has been approved by the American College of Rheumatology (ACR) Board of Directors. This signifies that it has been quantitatively validated using patient data, and it has undergone validation based on an independent data set. All ACR-approved criteria sets are expected to undergo intermittent updates. The ACR is an independent, professional, medical and scientific society that does not guarantee, warrant, or endorse any commercial product or service.

Objective. To develop and validate new Juvenile Arthritis Disease Activity Score 10 (JADAS10) and clinical JADAS10 (cJADAS10) cutoffs to separate the states of inactive disease (ID), minimal disease activity (MiDA), moderate disease activity (MoDA), and high disease activity (HDA) in children with oligoarthritis and with rheumatoid factor–negative polyarthritis, based on subjective disease assessment by the treating pediatric rheumatologist.

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Methods. The cutoffs definition cohort was composed of 1,936 patients included in the multinational Epidemiology, Treatment and Outcome of Childhood Arthritis (EPOCA) study. Using the subjective physician rating as an external criterion, 4 methods were applied to identify the cutoffs: mapping, Youden index, 90% specificity, and maximum agreement. The validation cohort included 4,014 EPOCA patients, patients from 2 randomized trials, and 88 patients from the PharmaChild registry. Cutoff validation was conducted by assessing discriminative and predictive ability.

Results. The JADAS10 cutoffs were 1.4, 4, and 13, respectively, for oligoarthritis and 2.7, 6, and 17, respectively, for polyarthritis. The cJADAS10 cutoffs were 1.1, 4, and 12, respectively, for oligoarthritis and 2.5, 5, and 16, respectively, for polyarthritis. The cutoffs discriminated strongly among different levels of pain and morning stiffness, between patients who were and those who were not prescribed a new medication, and between different levels of improvement in clinical trials. Achievement of ID and MiDA according to the new JADAS cutoffs at least twice in the first year of disease predicted better outcome at 2 years.

Conclusion. The 2021 JADAS and cJADAS cutoffs revealed good metrologic properties in both definition and validation samples, and are therefore suitable for use in clinical trials and routine practice.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a chronic inflammatory disease with a widely variable clinical course and outcome (1). Persistently active disease and uncontrolled synovial inflammation may cause structural joint damage (2), which may in turn lead to serious impairment of physical function and have marked impact on the quality of life of children and their families (3,4). Thus, regular assessment of the level of disease activity in children with JIA is fundamental to monitor the course of the disease over time and the effectiveness of therapeutic interventions. A precise measurement of disease activity may also have prognostic implications. For instance, achievement of the state of inactive disease (ID) at least once in the first 5 years was found to be associated with lower levels of long-term damage and functional impairment (5). Furthermore, the time spent in the state of active disease in the first 2 years was the most significant factor associated with the duration of active disease over the following years (6).

In the last decade, the use of composite disease activity scores in JIA has gained increasing popularity. These tools enable an easy and pragmatic approach to the quantification of disease activity by providing a summary number on a continuous scale, which is calculated by calculating the simple arithmetic sum of the scores of their individual components. The first composite disease activity score for JIA was developed in 2009 and was named the Juvenile Arthritis Disease Activity Score (JADAS) (7). The JADAS includes the following 4 measures: physician global assessment of disease activity measured on a 0–10 visual analog scale (VAS), parent/patient global assessment of child well-being measured on a 0–10 VAS, count of joints with active disease among the total assessed (10, 27, or 71 joints depending on the version), and the erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) level (8), both normalized to a 0–10 scale. A simplified, 3-item version of the score called the clinical JADAS (cJADAS), which excludes the acute-phase reactants, was subsequently published (9). Among the different versions of the score, the JADAS10 and the cJADAS10 have been more widely adopted as they are simpler than and equally effective as the other versions.

Proper interpretation of the scores obtained with JADAS calculation requires the definition of criteria for identifying high and low levels of disease activity (10). Cutoff values to separate the states of ID, minimal disease activity (MiDA), moderate disease activity (MoDA), and high disease activity (HDA) were established for both the JADAS (11,12) and the cJADAS (13). These cutoffs were defined with reference to published criteria for clinically inactive disease (CID) (14) and MiDA (15). At the time of previous cutoff definition, these criteria were considered as the only available external reference. However, use of these criteria has some limitations. The published criteria for CID include 3 of the 4 items in the JADAS, all of which must be scored zero. Thus, the variability of the JADAS in a patient who meets the criteria for CID can only be due to the fourth component, i.e., the parent/patient global assessment of the child's well-being. Similar concerns could be raised with regard to the definition of MiDA and the related JADAS cutoffs. Previous cutoffs for HDA were based on the treatment choices made by the treating physician. Potential limitations of the latter approach are that therapeutic choices may be driven by factors other than disease activity and that therapeutic decisions may vary across pediatric rheumatologists practicing in diverse geographic settings or with different clinical experience.

In a recently completed project (16), a large multinational cohort of JIA patients was enrolled and data collected on the treating physician's subjective rating of disease activity. In the present study, we took advantage of this large data set to develop and test new JADAS10 and cJADAS10 cutoffs for oligoarthritis and rheumatoid factor (RF)–negative polyarthritis disease activity states based on the subjective perception of international pediatric rheumatologists.

PATIENTS AND METHODS

Patient population used for the development of JADAS cutoffs. The cutoff definition cohort was selected from among the consecutive JIA patients included in the multinational Epidemiology, Treatment and Outcome of Childhood Arthritis (EPOCA) study (16), whose aims were to investigate the prevalence of JIA categories in different geographic areas, to gain

information on the treatments prescribed by international pediatric rheumatologists, and to assess the disease and health status of children with JIA living in diverse parts of the world. The EPOCA study included 9,081 patients enrolled in 49 countries between April 4, 2011 and November 21, 2016. For the purpose of the study, each JIA patient underwent a cross-sectional visit, during which the treating physician was asked to subjectively rate the disease status as ID, MiDA, MoDA, or HDA.

The oligoarthritis cutoff definition cohort consisted of the patients enrolled at the 20 centers that provided the largest sample of patients with persistent oligoarthritis. The number of oligoarthritis patients in each center ranged from 35 to 65. The polyarthritis cutoff definition cohort consisted of the patients enrolled at the 20 centers that provided the largest sample of patients with extended oligoarthritis and RF-negative polyarthritis. The number of polyarthritis patients in each center ranged from 35 to 65.

Patient populations used for the validation of JADAS cutoffs. Patients in the EPOCA study who had oligoarthritis or polyarthritis according to the International League of Associations for Rheumatology categorization (17) (subclassified as above) and who were not part of the cutoff definition cohort were included in the cutoff validation cohort. In addition, we obtained longitudinal data from 2 randomized clinical trials. The first (the TRIMECA trial [Comparison of the Efficacy of Intraarticular Corticosteroid Therapy Administered Alone or in Combination with Methotrexate in Children with JIA]) was a multicenter randomized clinical trial conducted in Italy between July 7, 2009 and March 31, 2013, which compared intraarticular glucocorticoid injections alone versus intraarticular glucocorticoid injections plus methotrexate in the treatment of oligoarticular JIA in a study population of 207 patients (18). The second was a randomized controlled trial conducted between February 2004 and June 2006, which assessed the efficacy and safety of abatacept withdrawal versus continuation in 190 patients with JIA (19). In the latter data set, only patients with extended oligoarticular arthritis and RF-negative polyarthritis were considered for cutoff validation.

To assess predictive ability, a fourth sample of patients was obtained from PharmaChild (20), a multinational registry to assess the long-term safety and efficacy of medications in children with JIA. We included all patients who had undergone at least 4 prospective visits in the first year of observation and a complete clinical assessment at 2 years after enrollment.

Methods used to calculate the cutoffs. The methodology for the definition of rheumatoid arthritis disease activity states based on the Clinical Disease Activity Index (CDAI) and the Simplified Disease Activity Index (SDAI) (10) was adapted for the present study. The following 4 methods were used to identify cutoffs in the JADAS10 and cJADAS10 to distinguish the states of ID, MiDA, MoDA, and HDA in oligoarthritis and RF-negative polyarthritis: mapping, Youden index, 90% specificity, and agreement.

The median of the values obtained with the 4 methods was retained as the cutoff for each disease activity state. For these analyses, we used the *OptimalCutpoints* package for R statistics, version 3.3.3 (21). This application computes optimal cut points for diagnostic tests or continuous markers and allows for selection of different approaches.

Mapping. For definition of the cutoff separating the states of ID and MiDA, the 75th percentile values of the JADAS10 and cJADAS10 in patients judged by their treating physician as having ID were retained. For definition of the cutoff separating the states of MiDA and MoDA, the 75th percentile values of the JADAS10 and cJADAS10 in patients judged as having ID or MiDA were retained. For definition of the cutoff separating the states of MoDA and HDA, the 25th percentile values of the JADAS10 and cJADAS10 in patients judged by their treating physician as having HDA were retained. Since for this analysis we considered it important to assign the same weight to each center regardless of the number of patients studied at the center, the cutoff values were retained separately for each center. The 20 values obtained for each cutoff were then averaged.

Youden index. The Youden index (J) identifies the maximum potential effectiveness of a biomarker through receiver operating characteristic (ROC) curve analysis. It is calculated with the formula $J = \max_c = (Se_c + Sp_c - 1)$, where \max_c is the maximally effective cutoff, Se_c is the cutoff with the maximum sensitivity, and Sp_c is the cutoff with the maximum specificity. The cutoff that achieves this threshold is considered the best cutoff because it is the one that optimizes the discriminative ability of the evaluated parameter when sensitivity and specificity are weighted equally (22,23). For each of the 3 cutoffs, patients were divided into 2 mutually exclusive groups, coded as 0 or 1. For the cutoff separating ID from MiDA, the first group comprised patients judged as having ID by the attending physician and the second comprised patients judged as having MiDA, MoDA, or HDA; for the cutoff separating MiDA from MoDA, the first group comprised patients judged as having ID or MiDA and the second comprised patients judged as having MoDA or HDA; for the cutoff separating MoDA from HDA, the first group comprised patients judged as having ID, MiDA, or MoDA and the second comprised patients judged as having HDA.

Ninety percent fixed specificity. With the 90% fixed specificity method, the 3 values identifying the states of ID, MiDA, MoDA, and HDA were obtained by fixing the specificity at 90% in the ROC curve analysis and considering the attending physician rating as the gold standard. This approach was chosen to minimize the rate of misclassification of patients with moderate/high disease activity as having inactive disease (24,25).

Evaluation of agreement. The analysis of agreement was based on the kappa statistic, which assesses the agreement beyond chance between 2 dichotomous ratings, using *OptimalCutpoints* for R statistics. The first rating was obtained using all

Table 1. JADAS10 and cJADAS10 cutoff values for classification of disease activity in children with juvenile idiopathic arthritis (oligoarthritis or polyarthritis) according to 4 different methods for determining optimal cutoffs*

Diagnosis, disease state distinction, JADAS version	Method for optimal cutoff determination						Median#	Sensitivity of chosen cutoff value	Specificity of chosen cutoff value	AUC
	75th percentile†	Youden index‡	90% specificity§	Kappa¶	90% specificity§	Kappa¶				
Oligoarthritis										
ID to MIDA										
JADAS10	1.5	1.2	1.9	1.2	1.4	76.1	93.6	0.919		
cJADAS10	1.2	1.0	1.5	1.0	1.1	79.5	92.9	0.922		
MIDA to MoDA										
JADAS10	3.9	4.0	4.2	9.2	4.0	77.4	90.7	0.923		
cJADAS10	3.4	4.0	3.5	6.5	4.0	80.5	87.0	0.924		
MoDA to HDA										
JADAS10	14.4	12.5	10.5	18.0	13.0	83.3	95.9	0.974		
cJADAS10	14.3	10.0	9.5	15.0	12.0	76.2	95.0	0.971		
Polyarthritis										
ID to MIDA										
JADAS10	2.6	2.7	2.3	3.0	2.7	79.1	90.2	0.925		
cJADAS10	2.5	2.5	2.0	3.0	2.5	81.0	89.0	0.924		
MIDA to MoDA										
JADAS10	5.1	5.9	5.9	9.9	6.0	79.8	88.6	0.927		
cJADAS10	5.0	5.0	5.0	7.5	5.0	76.0	92.2	0.924		
MoDA to HDA										
JADAS10	18.9	11.0	12.5	21.0	17.0	82.6	93.3	0.961		
cJADAS10	19.0	10.5	12.5	19.0	16.0	81.5	93.9	0.960		

* JADAS10 = Juvenile Arthritis Disease Activity Score 10; cJADAS10 = clinical JADAS10; AUC = area under the receiver operating characteristic curve; ID = inactive disease; MIDA = minimal disease activity; MoDA = moderate disease activity; HDA = high disease activity.

† Cutoff according to the 75th percentile of the cumulative score distribution.

‡ Cutoff according to the Youden index (22,23), that best distinguishes between patients divided into 2 mutually exclusive groups coded as 0 or 1.

§ Cutoff according to fixed 90% specificity.

¶ Cutoff with best agreement according to kappa analysis.

Median value among tentative cutoffs and chosen cutoff value.

possible JADAS10 and cJADAS10 values as hypothetical test criteria. To obtain the second rating, the categorical ratings from each attending physician (ID, MiDA, MoDA, or HDA) were dichotomized and were coded as 0 or 1, using the same approach as in the Youden index analysis. The software calculates the cutoff value with the highest kappa statistic.

Analyses performed to validate the cutoffs. Cutoff validation was based on assessment of discriminative and predictive ability. We tested whether the disease activity states according to the new cutoffs could discriminate 1) between patients in a cross-sectional sample with differing levels of various health outcomes, and 2) among different levels of response to a new treatment in 2 randomized clinical trials. Then, we tested the ability of JADAS10 and cJADAS10 states in the first year to predict clinically inactive disease at 2 years.

Ability to discriminate between different health states. In the EPOCA study, the median and interquartile range (IQR) level of pain on a 0–10-cm VAS (0 = no pain; 10 = maximum possible pain), the median and IQR count of joints with restricted function, the median level of physical function measured with the Juvenile Arthritis Functional Ability Scale (26) (range 0–45, where 0 is normal physical function), the percentage of parents who reported being not satisfied with current disease outcome, the percentage of patients with morning stiffness lasting >15 minutes, and the percentage of patients who were prescribed a new therapy for JIA at the study visit were compared across disease activity states defined by JADAS10 and cJADAS10 cutoffs. It was predicted that the values of all the above parameters would increase progressively from ID to HDA, although the changes in physical function and count of joints with restricted function were expected to be less pronounced as these indicators are affected by both disease activity and damage. Quantitative measures were compared by Kruskal-Wallis test with Dunn's post hoc test. Percentages were compared by chi-square test, with Bonferroni correction used for post hoc analysis.

Ability to discriminate among different levels of improvement. Patients at the 4-month visit in the open-label portion of the abatacept trial and at the 3-month visit in the TRIMECA trial were divided, according to the level of the American College of Rheumatology (ACR) Pediatric (Pedi) response (27), into 6 mutually exclusive groups: nonresponders, and ACR Pedi 30, 50, 70, 90, and 100 responders. For each level of response, we calculated the proportion of patients with ID, MiDA, MoDA, and HDA according to the new JADAS cutoffs. We expected that the proportion of patients with ID, MiDA, and MoDA would increase and that the proportion of patients with HDA would decrease when a higher level of improvement was met (moving from nonresponders to ACR Pedi 100 responders). We also expected that in both trials a higher proportion of patients would have had JADAS10 and cJADAS10 scores above the cutoffs for HDA cutoffs at the baseline visit.

Ability to predict future disease outcome. Among subjects in the PharmaChild registry, we compared the median and IQR number of visits with JADAS10 and cJADAS10 scores below the cutoffs for ID and MiDA and above the cutoffs for HDA in the first year of observation between patients who were and those who were not categorized as having CID according to the 2011 ACR JIA criteria (14) at 2 years. We also compared, using the same end point, the percentage of patients who had and those who did not have 2 or more visits with ID, MiDA, or HDA in the first year of observation. We expected that patients whose disease was clinically inactive at 2 years according to the ACR JIA criteria would have a higher number of visits with ID or MiDA and a lower number of visits with HDA in the first year. The inclusion of the state of MoDA was not considered meaningful for this analysis, because it was not expected that the number of visits in this intermediate state could predict the disease outcome.

Comparison with 2012–2014 cutoffs. The analyses described above were repeated using cutoffs published in 2012–2014 (11–13), and the statistical performance of the older versus the newer set of criteria was compared for each analysis (see below). The complete results of comparative validation of 2012–2014 cutoffs are presented in the Supplementary Appendix,

Table 2. Disease activity states based on the JADAS10 and cJADAS10, according to 2021 cutoffs and 2012–2014 cutoffs*

Disease activity state	2021 cutoffs		2012–2014 cutoffs	
	JADAS10	cJADAS10	JADAS10	cJADAS10
Oligoarthritis				
Inactive disease	≤1.4	≤1.1	≤1	≤1
Minimal disease activity	1.5–4	1.2–4	1.1–2	1.1–1.5
Moderate disease activity	4.1–13	4.1–12	2.1–4.2	1.51–4
High disease activity	>13	>12	>4.2	>4
Polyarthritis				
Inactive disease	≤2.7	≤2.5	≤1	≤1
Minimal disease activity	2.8–6	2.6–5	1.1–3.8	1.1–2.5
Moderate disease activity	6.1–17	5.1–16	3.9–10.5	2.51–8.5
High disease activity	>17	>16	>10.5	>8.5

* JADAS10 = Juvenile Arthritis Disease Activity Score 10; cJADAS10 = clinical JADAS10.

available on the *Arthritis & Rheumatology* website at <http://onlinelibrary.wiley.com/doi/10.1002/art.41879/abstract>.

RESULTS

Definition of cutoffs. The cutoff selection cohort comprised 979 patients with oligoarthritis and 957 patients with polyarthritis. Demographic and clinical features of the patients are shown in Supplementary Table 1, on the *Arthritis & Rheumatology* website at <http://onlinelibrary.wiley.com/doi/10.1002/art.41879/abstract>.

The JADAS10 and cJADAS10 cutoffs obtained with the 4 different statistical approaches and the final 3 cutoffs, calculated as the median of the 4 values to define the 4 disease states (ID, MiDA, MoDA, and HDA) in oligoarthritis and polyarthritis, are shown in Table 1. Table 2 presents the comparison of the current proposed cutoffs (2021 cutoffs) with cutoffs published in 2012–2014 (11–13). All of the 2021 cutoffs were higher than the 2012–2014 cutoffs.

Validation of cutoffs. *Ability to discriminate between different health states.* A total of 1,859 and 2,155 patients with oligoarthritis and polyarthritis, respectively, from the EPOCA study were included in this analysis; demographic and clinical features are

shown in Supplementary Table 1. The level of pain increased progressively from ID through HDA in both patient groups, based on either JADAS10 or cJADAS10 cutoffs (Figure 1). Likewise, the count of joints with restricted function and the physical function score worsened progressively throughout the same states ($P < 0.001$). However, Dunn's post hoc test revealed that among patients with oligoarthritis, only pain and physical function were different between all 4 disease activity states ($P < 0.001$ for all comparisons), whereas the count of joints with restricted function did not differ between patients with ID and patients with MiDA ($P = 0.18$ for JADAS10, $P = 0.14$ for cJADAS10). The proportion of patients not satisfied with illness outcome and the proportions of patients with morning stiffness and with newly prescribed medications at the time of the visit increased progressively from ID through HDA (Figure 2).

In the same data sets, using 2012–2014 cutoffs for oligoarthritis, the level of pain and functional ability and the count of joints with restricted function were not significantly different between patients with MiDA and patients with MoDA, for both the JADAS10 and the cJADAS10 (Figure 1 in the Supplementary Appendix, on the *Arthritis & Rheumatology* website at <http://onlinelibrary.wiley.com/doi/10.1002/art.41879/abstract>). Using the 2021 cutoffs, all comparisons in post hoc analyses of polyarthritis were significant.

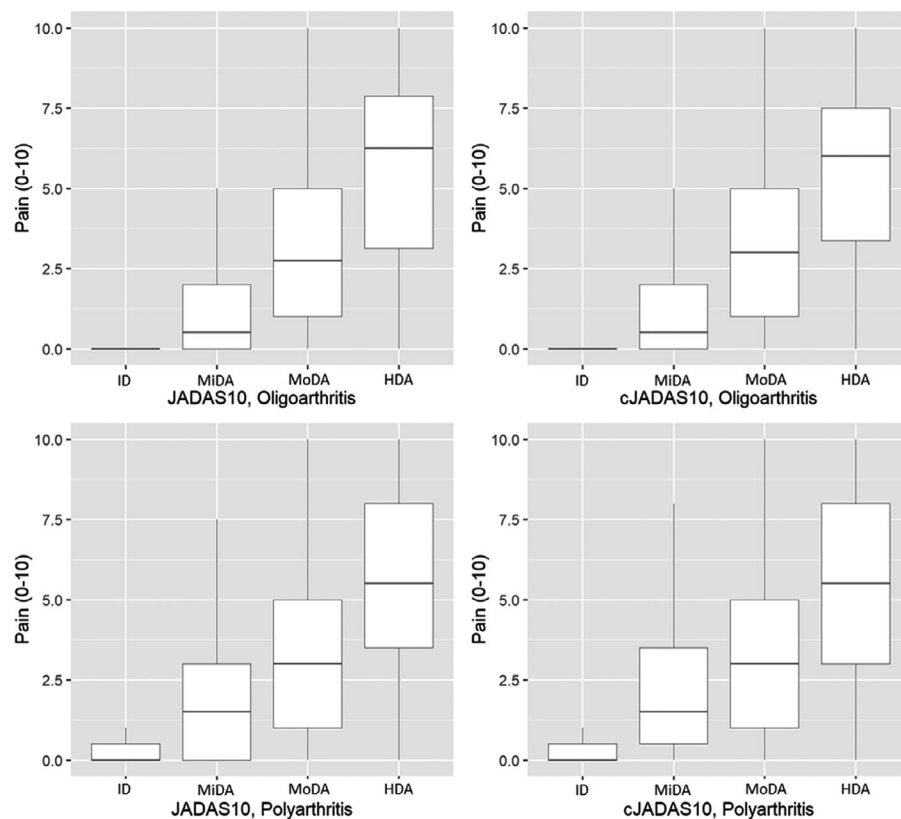


Figure 1. Comparison of the level of pain, measured on a 21-point 0–10 Likert scale, at visits ($n = 1,908$ for oligoarthritis and 2,489 for polyarthritis) in the Epidemiology, Treatment and Outcome of Childhood Arthritis study among patients with Juvenile Arthritis Disease Activity Score 10 (JADAS10)– and clinical JADAS10 (cJADAS10)–based inactive disease (ID), those with minimal disease activity (MiDA), those with moderate disease activity (MoDA), and those with high disease activity (HDA). Data are presented as box plots, where the boxes represent the 25th to 75th percentiles, the lines within the boxes represent the median, and the lines outside the boxes represent the range. $P < 0.001$ for comparison of disease states.

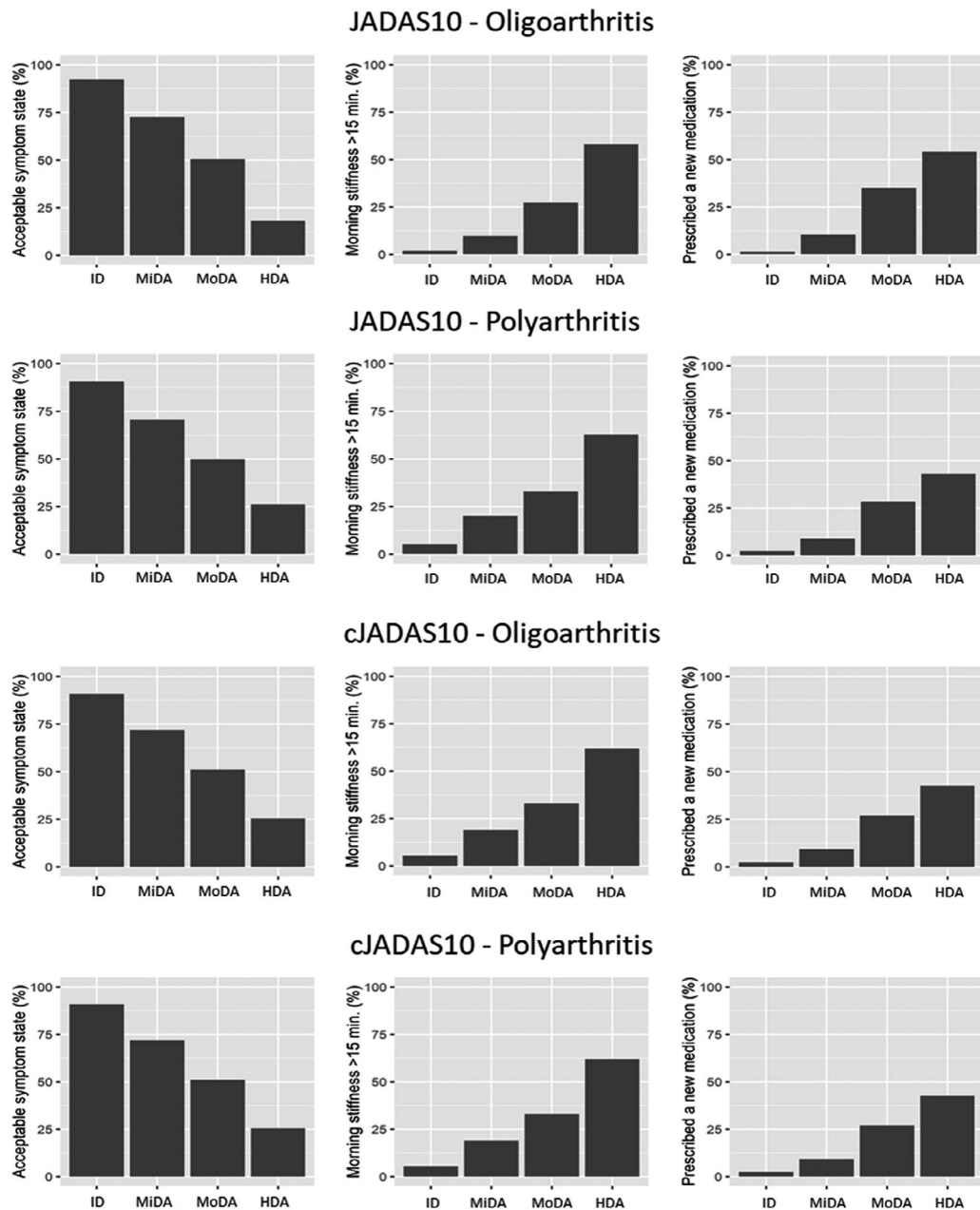


Figure 2. Percentage of patients whose parents described the patient's symptom status as acceptable, who had morning stiffness of >15 minutes, and who were prescribed a new medication for juvenile idiopathic arthritis at visits ($n = 1,908$ for oligoarthritis and 2,489 for polyarthritis) in the Epidemiology, Treatment and Outcome of Childhood Arthritis study among patients with Juvenile Arthritis Disease Activity Score 10 (JADAS10)- and clinical JADAS10 (cJADAS10)-based inactive disease (ID), those with minimal disease activity (MiDA), those with moderate disease activity (MoDA), and those with high disease activity (HDA). In post hoc analyses with Bonferroni correction, all comparisons were significant at $P < 0.001$ with the following exceptions: $P = 0.04$ for the comparison of morning stiffness frequency in oligoarthritis patients between the cJADAS10 states of MiDA and MoDA, and $P = 0.37$ for the comparison of the frequency of new therapy prescription in oligoarthritis patients between the cJADAS10 states of MiDA and MoDA.

In oligoarthritis and polyarthritis, the frequency of new medication prescription was not different between patients with ID and patients with MiDA according to 2012–2014 cutoffs for JADAS10 and cJADAS10. Additionally, in oligoarthritis, the frequency of morning stiffness was not different between patients with MiDA and patients with MoDA according to 2012–2014 cutoffs for JADAS10 and cJADAS10 (Figure 2 in the Supplementary Appendix).

Ability to discriminate among different levels of improvement.

The analysis included 148 oligoarthritis patients enrolled in the TRIMECA trial and 99 polyarthritis patients included in the abatacept trial. In the TRIMECA trial, all patients who exhibited an ACR Pedi 30 response at 3 months met the JADAS10 cutoffs for MoDA, whereas none met the cutoffs for ID and MiDA; of the 51 patients who exhibited an ACR Pedi 100 response,

Table 3. JIA patients with JADAS10 and cJADAS10 below the cutoff for inactive disease, with JADAS10 and cJADAS10 below the cutoff for minimal disease activity, and with JADAS10 and cJADAS10 above the cutoff for high disease activity in at least 2 visits in the first year of PharmaChild registry participation, among those with and those without clinically inactive disease according to ACR criteria at 2 years*

Visits in the first year†	Active disease at 2 years (n = 44)	Clinically inactive disease at 2 years (n = 44)	P
≥2 with ID by JADAS10	12 (27.3)	37 (84.1)	<0.001
≥2 with ID by cJADAS10	13 (29.5)	38 (86.4)	<0.001
≥2 with MiDA by JADAS10‡	27 (61.4)	42 (95.5)	<0.001
≥2 with MiDA by cJADAS10‡	26 (59.1)	42 (95.5)	<0.001
≥2 with HDA by JADAS10	7 (15.9)	1 (2.3)	0.064
≥2 with HDA by cJADAS10	8 (18.2)	0 (0.0)	0.009

* Values are the number (%). JIA = juvenile idiopathic arthritis; JADAS10 = Juvenile Arthritis Disease Activity Score 10; cJADAS10 = clinical JADAS10; ACR = American College of Rheumatology; ID = inactive disease; MiDA = minimal disease activity; HDA = high disease activity.

† Only patients with at least 4 visits in the first year of PharmaChild registry participation were included.

‡ Including patients with ID.

65%, 98%, and 100% met the JADAS10 cutoffs for ID, MiDA, and MoDA, respectively (Supplementary Figure 1A, <http://online.library.wiley.com/doi/10.1002/art.41879/abstract>). Similar data were obtained with the cJADAS10 (Supplementary Figure 1B). Of note, 1 patient in whom ID was achieved according to the JADAS10 and cJADAS10 was considered a nonresponder according to the ACR Pedi definition, due to an increase in the number of joints with limitation and a worsening in the level of physical function. The percentages of patients with JADAS10 and cJADAS10 above the cutoffs for HDA at trial baseline were 49% and 51%, respectively.

In the abatacept trial, 0%, 6%, and 56% of the patients with an ACR Pedi 30 response at 4 months met the JADAS10 cutoffs for ID, MiDA, and MoDA, respectively (Supplementary Figure 1C, <http://onlinelibrary.wiley.com/doi/10.1002/art.41879/abstract>); of those who exhibited an ACR Pedi 70 response, 31%, 75%, and 100% met the JADAS10 cutoffs for ID, MiDA, and MoDA, respectively. Findings with the cJADAS10 were similar (Supplementary Figure 1D). The percentages of patients with JADAS10 and cJADAS10 scores above the cutoffs for HDA at trial baseline were 63% and 68%, respectively.

According to 2012–2014 cutoffs, at least 50% of the patients with an ACR Pedi 30 to ACR Pedi 90 response in the TRIMECA trial would be classified as having HDA. In the abatacept trial, the percentage of patients with MiDA among patients who were ACR Pedi 70 responders according to 2012–2014 cutoffs did not exceed 40% (Figure 3 in the Supplementary Appendix, <http://online.library.wiley.com/doi/10.1002/art.41879/abstract>).

Ability to predict future disease outcome. The PharmaChild longitudinal sample included 88 patients, 33 of whom had persistent oligoarthritis. Among the patients with CID (n = 44) and those without CID (n = 44) by ACR JIA criteria at 2 years, the median number of visits with a JADAS10 score below the cutoff for ID, a JADAS10 score below the cutoff for MiDA, and a JADAS10 score above the cutoff for HDA, respectively, in

the first year was 4 (IQR 2–5), 5 (IQR 4–5), and 0 (IQR 0–0) in those whose disease was clinically inactive at 2 years, and 1 (IQR 0–2), 3 (IQR 1–4), and 0 (IQR 0–1) in those whose disease was not clinically inactive at 2 years ($P < 0.001$, $P < 0.001$, and $P = 0.031$, respectively). Similar results were obtained with the cJADAS10 (data not shown). Among the patients with CID according to the ACR criteria at 2 years, the percentage of visits in the first year in which the patient had ID or MiDA was higher, and the percentage in which the patient had HDA was lower, compared to the percentages among patients whose disease was active at 2 years (Table 3). Results from the same analysis performed using 2012–2014 cutoffs are shown in Table 1 in the Supplementary Appendix.

DISCUSSION

In this study, we defined cutoffs in the JADAS10 and cJADAS10 that correspond to the states of ID, MiDA, MoDA, and HDA in juvenile oligoarthritis and RF-negative polyarthritis, based on the subjective perception of disease activity level by pediatric rheumatologists from different regions of the world. We propose that the new cutoffs be called the 2021 JADAS10 and cJADAS10 cutoffs, to distinguish them from the previous cutoffs developed in 2012 and 2014 (11–13). Cutoff development was conducted using a large multinational data set comprising nearly 2,000 patients enrolled in 35 pediatric rheumatology centers located in 49 countries on 5 continents. The large sample size and the wide geographic distribution of the centers make the study findings likely generalizable to patients with various JIA phenotypes and treated with different approaches. Notably, the new cutoffs are closer to the JADAS thresholds identified by Swart et al for treatment escalation from a cohort of JIA patients seen at an academic center (28).

We considered it necessary to develop new cutoff values because previous JADAS and cJADAS cutoffs were developed

using formal criteria for CID (14) and MiDA (15) as reference standards, but both of these definitions comprise some JADAS components, making it difficult to avoid circular reasoning. Indeed, the definition of CID includes the count of joints with active arthritis, the physician global assessment of disease activity, and measurement of an acute-phase reactant. The definition of MiDA is centered on the count of joints with active arthritis, the physician global assessment of disease activity, and the parent/patient assessment of well-being. Another limitation of 2012–2014 cutoffs was the use of the physician's treatment decisions, collected retrospectively, as an external criterion. This approach did not take into account the fact that treatment changes could be driven by factors other than disease activity, such as drug intolerance or increased body weight. Furthermore, therapeutic choices may vary between physicians from different regions and according to their particular expertise and local availabilities of treatments.

For definition of the cutoffs, we adapted the methodology used by Aletaha et al (10) for the establishment of the CDAI and SDAI cutoffs. However, unlike that study, in which physicians rated multiple hypothetical patient profiles, we performed a more direct assessment by capturing disease activity ratings using actual patients. Because the proposed 2021 cutoffs are derived from real-life perception of patient disease activity by treating physicians, they may have greater face validity and practical relevance than the 2012–2014 cutoffs. The cutoff values were obtained by applying 4 different methods; of note, the tentative cutoffs yielded by agreement analysis were consistently higher than those yielded by different approaches, with the exception of the cutoff separating ID from MiDA. While the new cutoffs for distinguishing between ID and MiDA are very close to previous ones for oligoarthritis, they appear to be less stringent for polyarthritis. All cutoffs for the other disease activity states are notably higher in the new set.

The new cutoffs were validated using 4 different samples, including nearly 5,000 JIA patients. In cross-validation analyses, cutoff values differentiated well between levels of disease severity, as measured in terms of pain and count of joints with restricted function, and between patients who had or did not have morning stiffness or whose parents were satisfied or not satisfied with the outcome of the illness. In addition, the cutoffs revealed a strong ability to discriminate between different levels of ACR Pedi response in 2 randomized clinical trials. Notably, the cutoff values separating ID from MiDA in polyarthritis were met in a sizable proportion of cases only among patients with at least an ACR Pedi 70 response, which is in accordance with our previous findings that only an improvement in symptoms of at least 70% makes a substantial difference in disease status in patients with JIA (5). Nearly all ACR Pedi 100 responders with polyarthritis and the large majority with oligoarthritis met the cutoffs for ID. Finally, in the PharmaChild registry, achievement of the new cutoffs in the first year of observation was found to predict the attainment of disease remission at 2 years.

Our results should be interpreted in light of some potential caveats. The assessors were not provided any background

information on the definition of the various disease states that could help to enhance standardization of assessments. Furthermore, although the wide geographic representation of the pediatric rheumatologists who provided their ratings is a strength of our study, it could be argued that perception of disease activity may vary between physicians practicing in different regions or with diverse expertise and treatment availability. However, the fact that the reported cutoffs were based on the judgment of physicians from a large number of countries may lead to their widespread acceptance and use and foster the harmonization of clinical assessment in JIA. In addition, we decided to limit our study only to oligoarthritis and RF-negative polyarthritis owing to the wide clinical homogeneity between these 2 JIA categories. The application of the new cutoffs in different JIA categories, and in particular to RF-positive patients, who are included in most clinical trials on polyarthritis, requires validation. Recently, a systemic JIA-specific version of the JADAS was developed and validated (29), and cutoffs specific to this tool are needed. Finally, it must be acknowledged that part of the validation analysis (predictive ability assessment and ability to discriminate among different levels of improvement) was performed in a smaller subset of patients.

The comparison of the newer versus the older sets of criteria showed a better discriminative ability with the 2021 cutoffs, particularly for oligoarthritis. Moreover, the disease activity states based on the new cutoffs appear more consistent with the response to treatment defined with the ACR Pedi criteria in 2 clinical trials. In the comparison of predictive ability, the performances of cutoffs for inactive disease were similar. Compared to use of the 2012–2014 cutoffs, the percentage of patients with active disease at 2 years was relevantly higher among those who had at least 2 visits with a JADAS score below the cutoff for MiDA in the first year according to the 2021 cutoffs. Among patients with HDA at ≥ 2 visits in the first year according to 2021 cutoffs, a lower proportion had clinically inactive disease at 2 years.

In conclusion, we have developed a new set of JADAS10 and cJADAS10 cutoffs for the different disease activity states in JIA, which were based on the subjective perception of the level of disease activity by a multinational sample of pediatric rheumatologists. In validation analyses, the cutoffs demonstrated a strong ability to discriminate between different levels of disease severity and treatment response and to predict the achievement of long-term disease remission. Future studies should assess the 2021 cutoffs in other prospective patient cohorts and compare their metrologic performances to those of the 2012–2014 cutoffs.

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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. Consolaro 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.

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