

# Defining Criteria for Disease Activity States in Systemic Juvenile Idiopathic Arthritis Based on the Systemic Juvenile Arthritis Disease Activity Score

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**Objective.** Our objective was to develop and validate cutoff values in the systemic Juvenile Arthritis Disease Activity Score 10 (sJADAS10) that distinguish the states of inactive disease (ID), minimal disease activity (MDA), moderate disease activity (MoDA), and high disease activity (HDA) in children with systemic juvenile idiopathic arthritis, based on subjective disease state assessment by the treating pediatric rheumatologist.

**Methods.** The cutoff definition cohort was composed of 400 patients enrolled at 30 pediatric rheumatology centers in 11 countries. Using the subjective physician rating as an external criterion, six methods were applied to identify the cutoffs: mapping, calculation of percentiles of cumulative score distribution, the Youden index, 90% specificity, maximum agreement, and receiver operating characteristic curve analysis. Sixty percent of the patients were assigned to the definition cohort, and 40% were assigned to the validation cohort. Cutoff validation was conducted by assessing discriminative ability.

**Results.** The sJADAS10 cutoffs that separated ID from MDA, MDA from MoDA, and MoDA from HDA were  $\leq 2.9$ ,  $\leq 10$ , and  $> 20.6$ , respectively. The cutoffs discriminated strongly among different levels of pain, between patients with and without morning stiffness, and among patients whose parents judged their disease status as remission or persistent activity or flare or were satisfied or not satisfied with current illness outcome.

**Conclusion.** The sJADAS cutoffs revealed good metrologic properties in both definition and validation cohorts and are therefore suitable for use in clinical trials and routine practice.

## INTRODUCTION

Systemic juvenile idiopathic arthritis (sJIA) accounts for 5% to 15% of all children diagnosed with JIA in Western countries, but it

is distinctly more prevalent in Southeast Asia, with reported frequencies higher than 30% in India, Thailand, and Japan.<sup>1</sup> It stands apart from the other categories of JIA, owing to the association of arthritis with prominent extra-articular manifestations,

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which include high-spiking fever, erythematous macular rash, generalized lymphadenopathy, hepatosplenomegaly, polyserositis, and anemia. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and counts of neutrophils and platelets are typically quite elevated, reflecting systemic inflammation.<sup>2,3</sup> Because of the emerging evidence that there are patients who possess the same clinical and biologic systemic features observed in sJIA but never develop arthritis, new classification criteria that do not require the presence of arthritis have been proposed.<sup>4</sup> Children with sJIA are uniquely susceptible to developing potentially life-threatening complications, namely macrophage activation syndrome<sup>5</sup> and inflammatory lung disease.<sup>6,7</sup> sJIA is regarded as the pediatric counterpart of adult-onset Still disease.<sup>8–10</sup>

sJIA is considered the most severe form of childhood arthritis and is the most difficult to treat. It is a heterogeneous condition, and its course and outcome are variable and unpredictable. Regular assessment of the level of disease activity is important because uncontrolled inflammation plays a major role in causing structural joint damage and physical functional disability or may herald the occurrence of macrophage activation syndrome or inflammatory lung disease. Accurate measurement of the state of disease activity may have prognostic significance because achievement or persistence of inactive disease (ID) in JIA has been associated with better long-term outlook.<sup>11,12</sup>

In the last decade, the Juvenile Arthritis Disease Activity Score (JADAS) has been widely used for the measurement of disease activity in children with JIA in clinical trials, observational studies, and quality improvement analyses.<sup>13–19</sup> Recently, a version specific to sJIA, named the systemic JADAS (sJADAS), has been developed and validated.<sup>20</sup> Besides the four components of the JADAS (physician global assessment of disease activity [PhGA], parent and patient global assessments of child's well-

being [PaGA], count of joints with active disease, and an acute-phase reactant), this tool includes a fifth item aimed to quantify the activity of systemic manifestations called the modified Systemic Manifestation Score (mSMS).

To facilitate the interpretation of scores obtained with sJADAS calculation, criteria (ie, cutoff values) are needed for defining various levels of sJIA activity. These criteria may provide simple and intuitive reference values for monitoring of the disease course over time in an individual patient or for comparing the disease status across single patients or patient groups. Furthermore, they may support selection of patients for enrollment into clinical trials as well as requirements for changes in therapies and for establishing therapeutic goals in the treat-to-target strategy. The cutoffs for the main disease activity states in children with forms of JIA without systemic manifestations were previously defined for the original JADAS.<sup>21–24</sup> This study was undertaken to determine and validate cutoff values in the sJADAS that distinguish the states of ID, minimal disease activity (MDA), moderate disease activity (MoDA), and high disease activity (HDA) in children with sJIA.

## PATIENTS AND METHODS

**Composition and calculation of the sJADAS version used in the study.** The sJADAS<sup>20</sup> combines the following five key measures of disease activity in sJIA: (1) PhGA, measured on a 21-point 0 to 10 numerical rating scale (NRS) (in which 0 = no activity and 10 = maximum activity); (2) PaGA, measured on a 21-point 0 to 10 NRS (in which 0 = best and 10 = worst); (3) count of joints with active disease, assessed in 10, 27, or 71 joints, depending on the version (sJADAS10, sJADAS27, or sJADAS71, respectively); (4) ESR or CRP, both normalized to a scale from 0 to 10; and (5) the mSMS, which includes the following seven clinical and/or

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laboratory features: (1) fever = 1 point if temperature  $>37.5\text{--}38^\circ\text{C}$ , fever = 2 points if temperature  $>38\text{--}39^\circ\text{C}$ , fever = 3 points if temperature  $>39\text{--}40^\circ\text{C}$ , and fever = 4 points if temperature  $>40^\circ\text{C}$ ; (2) evanescent erythematous rash = 1 point; (3) generalized lymphadenopathy (enlargement of more than three lymph node stations) = 1 point; (4) hepatomegaly and/or splenomegaly = 1 point; (5) serositis (pleuritis, pericarditis, or peritonitis) = 1 point; (6) anemia (hemoglobin level  $<9\text{ g/dL}$ ) = 1 point; and (7) platelet count  $>600 \times 10^9/\text{L}$  or ferritin level  $>500\text{ ng/mL}$  = 1 point. Fever was defined as the maximum temperature recorded in the 24 hours before the study visit. The mSMS ranges from 0 to 10, in which 0 represents the absence of systemic manifestations and 10 represents the maximum activity of systemic manifestations.

Among the different versions of the original JADAS, the one that includes the 10-joint reduced count (ie, JADAS10) is preferred by most investigators because it is simpler and equally as effective as the other versions. For these reasons, the sJADAS10 was used for the present study. All five items of this tool are scored on a 0 to 10 scale, which yields a total score ranging from 0 (no disease activity) to 50 (maximum disease activity).

**Patient population used for the development and validation of sJADAS cutoffs.** Participation in the study was proposed to all pediatric rheumatology centers that contributed to the previous study that led to the development and validation of the sJADAS.<sup>20</sup> Participating centers were asked to enroll all consecutive patients seen after the study start who had “definite” sJIA (ie, a disease that met the International League of Associations for Rheumatology [ILAR] criteria for sJIA<sup>25</sup>) or “probable” or “possible” sJIA (ie, a febrile disease that presented with the classical extra-articular features of sJIA but lacked overt arthritis). Patients with probable or possible sJIA would meet the newly proposed criteria for sJIA.<sup>4</sup> Each patient could be enrolled at any of the following four disease activity states: ID, MDA, MoDA, and HDA. However, an individual patient could contribute to the study with a maximum of four visits, one for each disease activity state. This meant that the same patient could not be assessed more than once in the same disease activity state.

Through random computer generation, 60% of the patients enrolled in the study were assigned to the definition cohort, and the remaining 40% were assigned to the validation cohort. In addition, patients included in the original study that led to the development and validation of sJADAS<sup>20</sup> were used for one specific validation analysis (see the following sections). Exclusion criteria included autoinflammatory illnesses, other febrile rheumatic disorders (eg, Kawasaki disease), and febrile disorders resembling sJIA but with known etiology. Patients with overt macrophage activation syndrome<sup>26</sup> or inflammatory lung disease<sup>6,7</sup> were also excluded. Patient enrollment was started in February 2022 and closed in January 2023. Ethical approval was obtained in all countries according to national rules.

**Clinical assessments.** For the purpose of the study, each patient underwent a routine clinical visit, during which the treating physician was asked to subjectively rate the disease activity state as ID, MDA, MoDA, or HDA. To foster harmonization and reliability of evaluations, a background definition for each disease activity state was provided as reference (Supplementary Table S1). The same physician was also asked to record patients' demographic data and to perform all assessments required to calculate the sJADAS10. Before the study visit, a parent was asked to rate the intensity of the child's pain on a 21-point 0 to 10 NRS scale (in which 0 = no pain and 10 = maximum pain), to report the presence or absence of morning stiffness  $>15$  minutes, to describe subjectively the disease status as remission or persistent activity or flare, and to declare their satisfaction or nonsatisfaction with current illness outcome. Study data were collected in a standardized case report form and entered in an electronic database at the coordinating center (Istituto Giannina Gaslini, Genoa, Italy).

**Methods used to calculate the cutoffs.** The methodology previously employed for the definition of JIA disease activity states based on the JADAS and clinical JADAS (cJADAS)<sup>21–24</sup> was adapted for the present study. The following six methods were used to identify cutoffs in the sJADAS10 to distinguish the states of ID, MDA, MoDA, and HDA in sJIA: mapping, calculation of percentiles of cumulative score distribution, the Youden index, 90% specificity, agreement, and receiver operating characteristic (ROC) curve drawing.

*Mapping.* For definition of the cutoff separating the states of ID and MDA, values below the 75th percentile of the sJADAS10 in patients judged by their treating physician as having ID were retained. For definition of the cutoff separating the states of MDA and MoDA, values below the 75th percentile of the sJADAS10 in patients judged by their treating physician as having ID or MDA were retained. For definition of the cutoff separating the states of MoDA and HDA, values greater or equal to the 25th percentile of the sJADAS10 in patients judged by their treating physician as having HDA were retained.

*Calculation of percentiles of cumulative score distribution.* With this method, the choice of the cutoffs was based on the calculation of the 25th, 40th, and 75th percentiles of the entire set of sJADAS10 values. Patients with sJADAS10 below the 25th percentile were considered as having ID, patients with sJADAS10 values below the 40th percentile were considered as having ID or MDA, and patients with sJADAS10 values greater than the 75th percentile were considered as having HDA. This way of calculating the cutoffs has the advantage of being independent of treating physician's judgment.

*The Youden index.* The Youden index (J) identifies the maximum potential effectiveness of a biomarker through ROC curve analysis. It is calculated with the formula  $J = \text{maxc} = (\text{Sens} + \text{Sp} - 1)$ , in which maxc is the maximally effective cutoff, Sens is the cutoff with the maximum sensitivity, and Sp 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.<sup>27,28</sup> For each of the three cutoffs, patients were divided into two mutually exclusive groups, coded as 0 or 1. For the cutoff separating ID from MDA, the first group comprised patients judged by the treating physician as having ID, and the second group comprised patients judged as having MDA, MoDA, or HDA; for the cutoff separating MDA from MoDA, the first group comprised patients judged as having ID or MDA, and the second group comprised patients judged as having MoDA or HDA; for the cutoff separating MoDA from HDA, the first group comprised patients judged as having ID, MDA, or MoDA, and the second group comprised patients judged as having HDA.

*Ninety percent fixed specificity and evaluations of agreement and ROC curve.* With the 90% fixed specificity method, the three values identifying the states of ID, MDA, MoDA, and HDA were obtained by fixing the specificity at 90% in the ROC curve analysis and considering the treating physician rating as the gold standard. This approach was chosen to minimize the rate of misclassification of patients with MoDA to HDA as having ID.

*Evaluations of agreement and ROC curve.* The analysis of agreement was based on the kappa statistic, which assesses the agreement beyond chance between two dichotomous ratings. The first rating was obtained using all possible sJADAS10 values as hypothetical test criteria. The categorical ratings obtained from each treating physician (ID, MDA, MoDA, or HDA) were considered as the gold standard and evaluated in terms of observed agreement and Cohen's kappa concordance index. The ROC curve analysis was made using the classic method described by Metz<sup>27</sup> in 1978 and by Hanley and McNeil<sup>28</sup> in 1982, considering the sJADAS10 score as the quantitative variable to be categorized and the treating physician evaluation of disease activity states as the gold standard to be compared with.

**Analyses performed to validate the cutoffs.** Cutoff validation was based on assessment of discriminative ability. We evaluated whether the disease activity states based on the sJADAS10 cutoffs could discriminate (1) among patients with different health states as assessed by their parents, (2) between patients meeting or not meeting the 2011 American College of Rheumatology provisional criteria for defining clinical ID (CID) in JIA (hereinafter defined as Wallace criteria for CID)<sup>29</sup> and those meeting the preliminary definition of MDA in JIA (hereinafter defined as Magni-Manzoni criteria for MDA),<sup>30</sup> and (3) among patients evaluated at the baseline visit in the previous study that led to develop and validate the sJADAS.<sup>20</sup>

*Ability to discriminate between different health states.* The level of pain, the percentage of patients with morning stiffness lasting >15 minutes, the percentage of parents who described their child's disease status as remission, and the percentage of

parents who reported being satisfied with the current disease outcome were compared across disease activity states defined by sJADAS10 cutoffs. It was predicted that the level of pain and the frequency of morning stiffness would increase progressively from ID to HDA, whereas the frequencies of remission and of satisfaction with illness outcome would decrease progressively from ID to HDA.

*Ability to discriminate between 2011 Wallace criteria for CID and Magni-Manzoni criteria for MDA.* We calculated the proportion of patients with ID, MDA, MoDA, and HDA according to the sJADAS10 cutoffs who met each of the above criteria. We expected that Wallace criteria for CID were only met by patients with sJADAS10-based ID and that Magni-Manzoni criteria for MDA were only met by patients with sJADAS10-based ID or MDA.

*Ability to discriminate between patients at baseline visit in the sJADAS validation study.* Because patients enrolled in this study had to have new-onset disease or a disease flare at the baseline visit, it was anticipated that HDA and MoDA cutoffs were met more frequently at this visit. Quantitative measures were compared by the Kruskal-Wallis test. Percentages were compared by the chi-square test or by Fisher's exact test, in cases of expected frequencies <5. All statistical tests were two sided, the  $\alpha$  error was set at 0.05, and the software R (version 4.2.3) and Stata (version 17; StataCorp) were used for all the statistical analyses.

## RESULTS

**Patient population.** The cutoff selection cohort comprised 378 patients with sJIA enrolled at 30 pediatric rheumatology centers located in 11 countries on 4 continents. Ten patients had probable or possible sJIA, and 22 patients were assessed in more than one disease activity state. Owing to their low number and for the sake of simplicity, patients with probable or possible sJIA were combined with those with definite sJIA; furthermore, the 22 visits made by the same patient in a different disease activity state were considered as referring to distinct patients, which made up a total patient cohort of 400. The demographic and clinical features of the patient cohort considered as a whole and divided by the disease activity state assigned by the treating physician are shown in Supplementary Table S2 and in Table 1, respectively. There were no differences in the same features between patients who met ILAR criteria for sJIA and those who did not, aside from the presence of arthritis, which, as expected, was present only in the former subgroup (Supplementary Table S3).

Overall, the study cohort possesses the typical characteristics of children with sJIA seen in pediatric rheumatology centers worldwide.<sup>1</sup> The ages at disease onset and at the time of the study visit were comparable across patients categorized in the different disease activity states, whereas the disease duration

**Table 1.** Demographic and clinical features of 400 patients with sJIA divided by disease activity state assessed subjectively by the treating physician\*

	Inactive disease (n = 150)	Minimal disease activity (n = 75)	Moderate disease activity (n = 87)	High disease activity (n = 88)
Demographic features				
Sex				
Male, n (%)	75 (50.0)	29 (38.7)	39 (44.8)	37 (42.0)
Female, n (%)	75 (50.0)	46 (61.3)	48 (55.2)	51 (58.0)
Age at onset, median (1st–3rd quartiles), y	5.2 (2.7–8.8)	4.2 (2.1–7.9)	4.8 (2.6–7.6)	3.9 (2.1–7.8)
Age at visit, median (1st–3rd quartiles), y	10.3 (6.7–14.3)	9.5 (5.4–13.3)	10.1 (4.9–13.1)	7.9 (4.4–12)
Disease duration, median (1st–3rd quartiles), y	3.5 (1.3–7.1)	3.4 (1–7)	3.3 (0.3–8)	0.6 (0.2–4.4)
Clinical outcome measures, median (1st–3rd quartiles)				
Physician global assessment <sup>a</sup>	0 (0–0)	1.5 (1–2.5)	6 (4–7)	8.5 (7.9–9)
Parent global assessment <sup>a</sup>	0 (0–0.5)	0 (0–2.5)	5 (2–7)	8 (5.5–9.5)
Count of active joints	0 (0–0)	0 (0–1)	3 (1–6)	5 (2–11.5)
sJADAS10 value <sup>b</sup>	0.5 (0–1.5)	4 (1.5–7.9)	20.4 (14.9–25.2)	31 (26.6–35.8)
Systemic manifestations, n (%)				
Fever <sup>c</sup>	0 (0)	0 (0)	39 (44.8)	82 (93.2)
Rash	0 (0)	5 (6.7)	21 (24.1)	47 (53.4)
Hepatomegaly	0 (0)	1 (1.3)	9 (10.3)	29 (33)
Splenomegaly	0 (0)	2 (2.7)	9 (10.3)	20 (22.7)
GLA	1 (0.7)	2 (2.7)	6 (6.9)	28 (31.8)
Serositis	0 (0)	0 (0)	6 (6.9)	10 (11.4)
Laboratory values, median (1st–3rd quartiles)				
Hemoglobin, g/dL	12.8 (12–13.7)	12.1 (11.3–13.1)	11.1 (10.1–12)	10.2 (9–11.2)
White blood cell count, ×10 <sup>9</sup> /L	6.9 (5.4–8.4)	8.4 (7–10.4)	9.8 (7–15)	12.8 (8.9–17.8)
Neutrophil count, ×10 <sup>9</sup> /L	3.1 (2.3–4.3)	4.2 (3–7)	5.9 (3.8–10.8)	8.3 (5–13.3)
Platelet count, ×10 <sup>9</sup> /L	283 (239–343)	320 (266–404)	396.5 (288–539)	426.5 (313–586)
Ferritin, ng/mL	36.7 (22–68.4)	53.1 (29.2–121)	236 (80–520)	494 (233–1,875)
ESR, mm/h	7 (3–12)	12 (4–21)	40 (22–70)	65 (42.5–92.8)
C-reactive protein, mg/dL	0.1 (0.1–0.4)	0.3 (0.1–0.6)	2.5 (0.7–6)	9.6 (3.3–16.6)
Fibrinogen, mg/dL	256 (211–307)	278.5 (229–382)	378 (261–461)	490 (365–592)

\* All comparisons were significant ( $P < 0.001$ ) except for sex ( $P = 0.36$ ) and age at onset ( $P = 0.15$ ). The age at the time of the visit was significantly different among the four groups ( $P = 0.015$ ). ESR, erythrocyte sedimentation rate; GLA, generalized lymphadenopathy; sJADAS10, systemic juvenile Arthritis Disease Activity Score 10; sJIA, systemic juvenile idiopathic arthritis.

<sup>a</sup> Measured on a 21-point 0–10 numerical rating scale, in which 0 = best and 10 = worst.

<sup>b</sup> Scores range from 0 = no activity to 50 = maximum activity.

<sup>c</sup> Body temperature  $> 37.5$  °C in the 24 hours before the visit.

was shorter in patients with HDA, reflecting the proximity to disease onset of most patients in this state. The frequency of active systemic symptoms and the values of outcome measures and laboratory indicators of inflammation increased or worsened progressively from ID to HDA groups. These trends testify the reliability of the evaluations made by the caring physicians who participated in the study. The main features of the 240 patients included in the definition cohort and of the 160 patients included in the validation cohort were comparable (Supplementary Table S4).

**Definition of cutoffs.** The sJADAS10 cutoffs obtained with the six different statistical approaches are shown in Table 2. As expected, the cutoffs for ID were the lowest, and the values increased progressively for the states of MDA, MoDA, and HDA. The following criteria were used to select the final cutoffs: specificity

was considered more relevant than sensitivity to identify the cutoffs for the states of ID and MDA and to reduce the risk of misclassifying patients whose disease was actually active. However, a minimum sensitivity of 75% was requested to ensure adequate face validity of the criteria. Conversely, in selecting the final cutoff values for HDA, we gave more importance to sensitivity, that is, to the proportion of patients with active disease who were correctly classified, to avoid misclassifying patients whose disease was active. However, a minimum specificity of 75% was required to minimize the rate of misclassification of patients with MDA or MoDA as having HDA. The final sJADAS10 cutoff values that were selected for the various disease activity states are shown in Table 3. There was a close correspondence between sJADAS10-based disease activity states and disease activity states defined subjectively by the treating physicians (Supplementary Figure S1).

**Table 2.** sjADAS10 cutoff values for classification of patients into disease activity states according to six different methods for determining optimal cutoffs\*

Disease activity state	Mapping 25th or 75th percentile <sup>a</sup> (sensitivity, specificity)	Youden index (sensitivity, specificity)	90% fixed specificity (sensitivity, specificity)	Agreement, Cohen's $\kappa$ (sensitivity, specificity)	25th, 40th, or 75th percentile <sup>b</sup> (sensitivity, specificity)	ROC curve (sensitivity, specificity)
ID to MDA	≤1.8 (75.3, 92.5)	≤3 (89.4, 89.7)	≤2.9 (85.9, 91.8)	≤3 (89.4, 89.7)	≤1 (67.1, 93.8)	≤3 (89.4, 89.7)
MDA to MoDA	≤3.5 (75.2, 97.2)	≤12 (98.4, 88.7)	≤10 (95.2, 91.5)	≤12 (98.4, 88.7)	≤3.5 (75.2, 97.2)	≤12 (98.4, 88.7)
MoDA to HDA <sup>c</sup>	>25.58 (75, 92.7)	>20.6 (94.2, 85.5)	>24.3 (82.7, 90.5)	>24.3 (82.7, 90.5)	≥24.8 (80.8, 91.1)	>20.6 (94.2, 85.5)

\* HDA, high disease activity; ID, inactive disease; MDA, minimal disease activity; MoDA, moderate disease activity; ROC, receiver operating characteristic; sjADAS10, systemic Juvenile Disease Activity Score 10.

<sup>a</sup> The 75th percentile was applied for calculation of the ID to MDA and MDA to MoDA cutoffs, whereas the 25th percentile was applied for calculation of the MoDA to HDA cutoff.

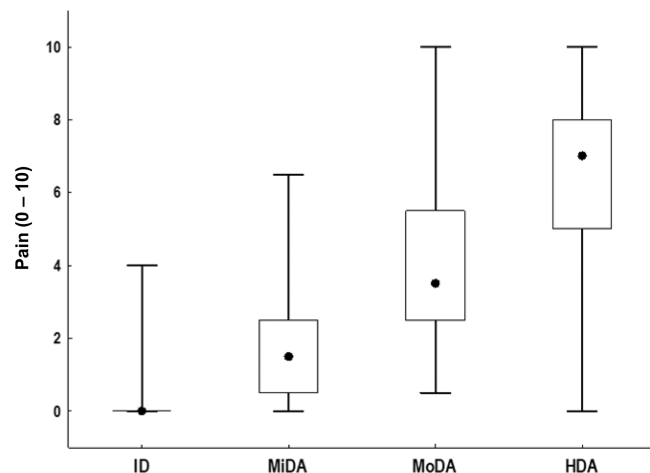
<sup>b</sup> The 25th percentile was applied for calculation of the ID to MDA cutoff, whereas the 40th percentile was applied for calculation of the MDA to MoDA cutoff, and the 75th percentile was applied for calculation of the MoDA to HDA cutoff.

**Table 3.** Proposed cutoff values for definition of sjADAS10-based disease activity states in sJIA\*

Disease activity state	Cutoff value	Method used to select the cutoff	Sensitivity, specificity	Criterion used to select the cutoff
ID to MDA	≤2.9	90% fixed specificity	85.9, 91.8	Highest specificity with sensitivity >85%
MDA to MoDA	≤10	90% fixed specificity	95.2, 91.5	Highest specificity with sensitivity >85%
MoDA to HDA	>20.6	ROC curve method	94.2, 85.5	Highest sensitivity with specificity >85%

\* HDA, high disease activity; ID, inactive disease; MDA, minimal disease activity; MoDA, moderate disease activity; sjADAS10, systemic Juvenile Arthritis Disease Activity Score 10; sJIA, systemic juvenile idiopathic arthritis.

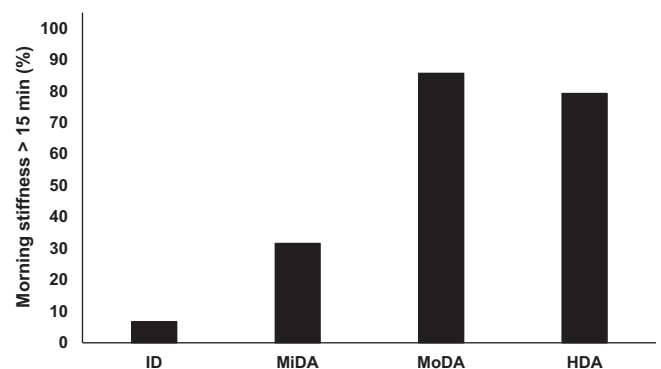
**Validation of cutoffs.** Ability to discriminate between different health states. The level of pain and the proportion of patients with morning stiffness >15 minutes increased progressively from ID to HDA (Figures 1 and 2). Conversely, the percentage of parents who reported being satisfied with the current



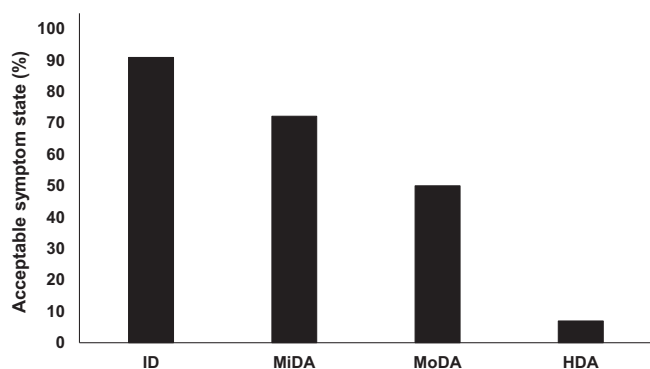
**Figure 1.** Comparison of the level of pain, measured on a 21-point, 0 to 10 numerical rating scale, at visit among patients with systemic Juvenile Arthritis Disease Activity Score 10–based ID, those with MDA, those with MoDA, and those with HDA. Data are presented as box plots, in which the boxes represent the 25th and 75th percentiles, the dots within the boxes represent median values, and the lines outside the boxes represent the range.  $P < 0.0001$  for comparison of disease states. HDA, high disease activity; ID, inactive disease; MDA, minimal disease activity; MoDA, moderate disease activity.

disease outcome or described their child's disease status as remission decreased progressively from ID to HDA (Figure 3 and Supplementary Figure S2).

Ability to discriminate between 2011 Wallace criteria for CID and Magni-Manzoni criteria for MiDA. Only 97 (63.8%) of the 152 patients who were classified as having ID by the sjADAS met the 2011 Wallace criteria for CID<sup>29</sup> (Supplementary Table S5). However, only 7 (3%) of the 235 patients who did not have ID based on the sjADAS met the Wallace criteria for CID (Supplementary Table S6). The reasons that prevented the 55 patients with



**Figure 2.** Percentage of patients who had morning stiffness of >15 minutes among patients with systemic Juvenile Arthritis Disease Activity Score 10–based ID, those with MDA, those with MoDA, and those with HDA.  $P < 0.0001$  for comparison of disease states. HDA, high disease activity; ID, inactive disease; MDA, minimal disease activity; MoDA, moderate disease activity.



**Figure 3.** Percentage of patients whose parents described the patient's symptom state as acceptable among patients with systemic Juvenile Arthritis Disease Activity Score 10–based ID, those with MDA, those with MoDA, and those with HDA.  $P < 0.0001$  for comparison of disease states. HDA, high disease activity; ID, inactive disease; MDA, minimal disease activity; MoDA, moderate disease activity.

sJADAS-based ID from meeting the CID definition were a PhGA  $>0$  ( $n = 31$ ), an elevated acute-phase reactant level ( $n = 29$ ), and/or a count of active joints  $>0$  ( $n = 3$ ) (Supplementary Figure S3). The reason that prevented all seven patients who met the CID definition from meeting the sJADAS ID definition was a PaGA  $\geq 3$  (range 3–7) (Supplementary Table S7). A better concordance was seen between Magni-Manzoni criteria for MDA<sup>30</sup> and sJADAS-based criteria for MDA (Supplementary Table S5).

Ability to discriminate between patients at baseline visit in the sJADAS validation study. Because patients enrolled in this study had to have new-onset disease or a disease flare at baseline visit, it was anticipated that HDA and MoDA cutoffs were met more frequently at this visit.<sup>20</sup>

## DISCUSSION

In this study, we determined the cutoffs in the sJADAS10 that correspond to the states of ID, MDA, MoDA, and HDA in sJIA, based on the subjective perception of disease activity level by pediatric rheumatologists practicing in different regions of the world. Cutoff definition was performed using a large multinational data set comprising 400 patients enrolled at 30 pediatric rheumatology centers in 11 countries and 4 continents. The large sample size and the wide geographic distribution of the centers make the study findings likely generalizable to patients with various sJIA phenotypes and treated with different approaches. To help enhance the standardization of assessments and minimize the impact of variability in perception of disease activity among physicians with diverse expertise, the assessors were provided with background information on the definition of the various disease states. The widening of enrollment to patients with a febrile disease who presented with the classical extra-articular features of sJIA but lacked overt arthritis is in keeping with the emerging evidence that these patients are part of the spectrum of sJIA.<sup>4</sup>

For the definitions of the cutoffs, we applied a methodology similar to that previously employed for the establishment of the JADAS and cJADAS cutoffs for disease activity states in JIA.<sup>21–24</sup> The selected cutoffs were those yielded by the 90% fixed specificity method for separation of ID from MDA and of MDA from MoDA and by the ROC curve method for separation of MoDA from HDA. In line with the requirements established a priori, the cutoffs for the states of ID and MDA had, besides a minimum fixed specificity of 90%, a sensitivity of 85.9% and 95.2%, respectively, and the cutoffs for the state of HDA had the best sensitivity (94.2%) and a specificity of 85.5%. These statistical requirements were deemed necessary to reduce the risk of misclassifying ID or MDA in patients whose disease was actually active, and thus could deserve an aggressive therapy, and to minimize the rate of misclassification of patients with MDA or MoDA as having HDA, thus avoiding overtreatment. The good performances of the cutoffs were corroborated a posteriori by their close association with the subjective assessment of the disease state made by the treating physicians from which they were derived.

In validation analyses, the cutoffs showed strong ability to discriminate among different health states based on the perception of parents living in different regions of the world. The cutoffs for ID and MDA were met more commonly by patients with no morning stiffness and by patients whose parents judged their disease status as remission or were satisfied with the current illness outcome. Conversely, the cutoffs for HDA were met more frequently by patients with morning stiffness and by patients whose parents judged their disease status as persistent activity or flare or were not satisfied with the illness outcome. The level of pain was lowest in patients who met the ID cutoffs and was proportionally greater in patients with MDA, MoDA, and HDA.

The cutoffs revealed only fair agreement with the Wallace criteria for CID<sup>29</sup> because around one-third of the patients who had ID based on the sJADAS10 did not meet the CID definition. This discordance may be explained by the stringency of Wallace criteria, which require a PhGA score of 0, an absence of active joints, and normal values of acute-phase reactants. Furthermore, these criteria do not incorporate the PaGA, which was found to be responsible for the poor overlap between the Wallace CID definition and JADAS ID criteria through an incongruous inflating effect on the JADAS, especially in the presence of persistent pain symptoms.<sup>31</sup> The reason that prevented patients who met Wallace CID definition from meeting sJADAS ID was, indeed, a PaGA above the sJADAS-based ID threshold in all observed instances, although this disparity was recorded in only seven (3%) of the patients. The fact that the PhGA was more frequently responsible than the count of active joints for preventing patients with sJADAS-based ID from meeting the CID definition is in keeping with our previous observation that many physicians tend not to mark a score of 0 for patients in whom they find to not have active joints.<sup>32</sup> The concordance was better between the sJADAS-

based criteria for MDA and the Magni-Manzoni criteria for MDA,<sup>30</sup> which were developed using the therapeutic decision made by the caring physician as the reference criterion. This finding suggests that deriving definitions of disease activity states from the real world of clinical practice enhances their face validity.

The face validity of the HDA cutoff was corroborated by the observation that it was met more commonly by patients assessed at baseline in the original sJADAS validation study, in which patients were candidate to receive an aggressive therapeutic intervention. This finding suggests that the sJADAS10-based HDA cutoff is suitable to select patients for enrollment in clinical trials.

Some caveats should be taken into account in interpreting our findings. Although we fostered harmonization of disease activity state evaluation across assessors by providing reference clinical definitions, it could be argued that the perception of disease activity may vary among physicians practicing in different regions or with diverse expertise and treatment availability. However, the fact that the reported cutoffs were based on the judgments of physicians from a large number of countries may lead to their widespread acceptance and use. Nevertheless, the potential impact of discrepant perceptions of disease activity depending on physician experience and practice setting should be investigated in the future for both the sJADAS cutoffs and the cutoffs that were previously created in the same way for nonsystemic forms of JIA. Because of the lack of longitudinal data sets with all variables needed to calculate the sJADAS10, we could not investigate the capacity of the cutoffs to predict disease outcomes, such as continued activity, cumulative damage, or functional disability, or the occurrence of major complications, such as macrophage activation syndrome or inflammatory lung disease. For the same reason, we could not investigate the performance of the cutoffs in the context of a randomized clinical trial in sJIA. These goals should be pursued in future investigations after dissemination of the cutoffs. Our effort did not take into account the recent scientific evidence for biomarkers of immune activation and systemic inflammation in sJIA.<sup>33</sup> Although these biomarkers are still not available on a routine basis, they will likely be included in future tools for disease activity assessment. A further limitation of the sJADAS is the inclusion of the height of the fever, which is not often recorded in either clinical notes or registries.

In conclusion, we have developed the criteria for the definition of disease activity states in sJIA based on the sJADAS10. The cutoffs were derived from real-life perceptions of patient disease activity by treating physicians, which may provide them with good face validity and practical relevance and foster the harmonization of clinical assessment in sJIA. In validation analyses, the cutoffs revealed a strong ability to discriminate among disease activity states defined subjectively by the parents as well as among different levels of pain or between the presence and absence of morning stiffness. Furthermore, they corresponded well with established criteria for CID and MDA in JIA. The cutoffs 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 disease 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.** Rosina, Rebollo-Giménez, Consolaro, Ravelli.

**Acquisition of data.** Rebollo-Giménez, Tarantola, Vyzhga, El Miedany, Lofty, Abu-Shady, Eissa, Osman, Hassan, Mahgoub, Fouad, Mosa, Adel, Mohamed, Radwan, Abu-Zaid, Tabra, Shalaby, Nasef, Khubchandani, Khan, Maldar, Ozen, Bayindir, Alsuweit, Alzyoud, Almaaitah, Vilaiyuk, Lerkvaleekul, Alexeeva, Dvoryakovskaya, Kriulin, Bracaglia, Pardeo, De Benedetti, Licciardi, Montin, Robasto, Minoia, Filocomo, Rossano, Simonini, Marrani, Abu-Rumeileh, Kostik, Belozarov, Pal, Bathia, Katsicas, Villarreal, Marino, Costi, Sztajn bok, Silva, Maggio, El-Ghoneimy, El Owaidy, Civino, Diomeda, Al-Mayouf, Al-Sofyani, Davidstone, Patrone, Saad-Magalhães.

**Analysis and interpretation of data.** Rosina, Tarantola, Pistorio, Patrone, Consolaro, Ravelli.

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## REFERENCES

1. Consolaro A, Giancane G, Alongi A, et al; Paediatric Rheumatology International Trials Organisation. Phenotypic variability and disparities in treatment and outcomes of childhood arthritis throughout the world: an observational cohort study. *Lancet Child Adolesc Health* 2019;3(4):255–263.
2. Martini A. Systemic juvenile idiopathic arthritis. *Autoimmun Rev* 2012; 12(1):56–59.
3. De Benedetti F, Schneider R. Systemic juvenile idiopathic arthritis. In: Petty R, Laxer R, Lindsley C, Wedderburn L, eds. *Textbook of pediatric rheumatology*. 7th ed. Elsevier; 2016:205–216.
4. Martini A, Ravelli A, Avcin T, et al; Pediatric Rheumatology International Trials Organization (PRINTO). Toward new classification criteria for juvenile idiopathic arthritis: first steps, Pediatric Rheumatology International Trials Organization International Consensus. *J Rheumatol* 2019;46(2): 190–197.
5. Minoia F, Davi S, Horne A, et al; Pediatric Rheumatology International Trials Organization; Childhood Arthritis and Rheumatology Research Alliance; Pediatric Rheumatology Collaborative Study Group; Histiocyte Society. Clinical features, treatment, and outcome of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a multinational, multicenter study of 362 patients. *Arthritis Rheumatol* 2014;66(11):3160–3169.
6. Saper VE, Chen G, Deutsch GH, et al; Childhood Arthritis and Rheumatology Research Alliance Registry Investigators. Emergent high fatality lung disease in systemic juvenile arthritis. *Ann Rheum Dis* 2019;78(12):1722–1731.
7. Schulert GS, Yasin S, Carey B, et al. Systemic juvenile idiopathic arthritis-associated lung disease: characterization and risk factors. *Arthritis Rheumatol* 2019;71(11):1943–1954.



8. Inoue N, Shimizu M, Tsunoda S, et al. Cytokine profile in adult-onset Still's disease: comparison with systemic juvenile idiopathic arthritis. *Clin Immunol* 2016;169:8–13.
9. Nirmala N, Brachat A, Feist E, et al. Gene-expression analysis of adult-onset Still's disease and systemic juvenile idiopathic arthritis is consistent with a continuum of a single disease entity. *Pediatr Rheumatol Online J* 2015;13(1):50.
10. Jamilloux Y, Georjin-Lavialle S, Sève P, et al. Le temps est venu de réconcilier l'arthrite juvénile idiopathique systémique et la maladie de Still de l'adulte. [It is time to reconcile systemic juvenile idiopathic arthritis and adult-onset Still's disease]. *Rev Med Interne* 2019;40(10):635–636.
11. Albers HM, Brinkman DM, Kamphuis SS, et al. Clinical course and prognostic value of disease activity in the first two years in different subtypes of juvenile idiopathic arthritis. *Arthritis Care Res (Hoboken)* 2010;62(2):204–212.
12. Magnani A, Pistorio A, Magni-Manzoni S, et al. Achievement of a state of inactive disease at least once in the first 5 years predicts better outcome of patients with polyarticular juvenile idiopathic arthritis. *J Rheumatol* 2009;36(3):628–634.
13. Consolaro A, Ruperto N, Bazso A, et al; Paediatric Rheumatology International Trials Organisation. Development and validation of a composite disease activity score for juvenile idiopathic arthritis. *Arthritis Rheum* 2009;61(5):658–666.
14. Ramanan AV, Quartier P, Okamoto N, et al; JUVE-BASIS investigators; Paediatric Rheumatology International Trials Organisation. Baricitinib in juvenile idiopathic arthritis: an international, phase 3, randomised, double-blind, placebo-controlled, withdrawal, efficacy, and safety trial. *Lancet* 2023;402(10401):555–570.
15. Ruperto N, Brunner HI, Synoverska O, et al; Paediatric Rheumatology International Trials Organisation (PRINTO) and Pediatric Rheumatology Collaborative Study Group (PRCSG). Tofacitinib in juvenile idiopathic arthritis: a double-blind, placebo-controlled, withdrawal phase 3 randomised trial. *Lancet* 2021;398(10315):1984–1996.
16. Brunner HI, Ruperto N, Tzaribachev N, et al; Paediatric Rheumatology International Trials Organisation (PRINTO) and the Pediatric Rheumatology Collaborative Study Group (PRCSG). Subcutaneous golimumab for children with active polyarticular-course juvenile idiopathic arthritis: results of a multicentre, double-blind, randomised-withdrawal trial. *Ann Rheum Dis* 2018;77(1):21–29.
17. Quartier P, Alexeeva E, Constantin T, et al; Paediatric Rheumatology International Trials Organisation and the Pediatric Rheumatology Collaborative Study Group. Tapering canakinumab monotherapy in patients with systemic juvenile idiopathic arthritis in clinical remission: results from a phase IIIb/IV open-label, randomized study. *Arthritis Rheumatol* 2021;73(2):336–346.
18. Brunner HI, Tzaribachev N, Louw I, et al; Paediatric Rheumatology International Trials Organisation (PRINTO) and the Pediatric Rheumatology Collaborative Study Group (PRCSG) investigators. Long-term maintenance of clinical responses by individual patients with polyarticular-course juvenile idiopathic arthritis treated with abatacept. *Arthritis Care Res (Hoboken)* 2023;75(11):2259–2266.
19. Bingham CA, Harris JG, Qiu T, et al; Pediatric Rheumatology Care and Outcomes Improvement Network. Pediatric rheumatology care and outcomes improvement network's quality measure set to improve care of children with juvenile idiopathic arthritis. *Arthritis Care Res (Hoboken)* 2023;75(12):2442–2452.
20. Tibaldi J, Pistorio A, Aldera E, et al. Development and initial validation of a composite disease activity score for systemic juvenile idiopathic arthritis. *Rheumatology (Oxford)* 2020;59(11):3505–3514.
21. Consolaro A, Bracciolini G, Ruperto N, et al; Paediatric Rheumatology International Trials Organization. Remission, minimal disease activity, and acceptable symptom state in juvenile idiopathic arthritis: defining criteria based on the juvenile arthritis disease activity score. *Arthritis Rheum* 2012;64(7):2366–2374.
22. Consolaro A, Ruperto N, Bracciolini G, et al; Paediatric Rheumatology International Trials Organization (PRINTO). Defining criteria for high disease activity in juvenile idiopathic arthritis based on the juvenile arthritis disease activity score. *Ann Rheum Dis* 2014;73(7):1380–1383.
23. Consolaro A, Negro G, Chiara Gallo M, et al. Defining criteria for disease activity states in nonsystemic juvenile idiopathic arthritis based on a three-variable juvenile arthritis disease activity score. *Arthritis Care Res (Hoboken)* 2014;66(11):1703–1709.
24. Trincianti C, Van Dijkhuizen EHP, Alongi A, et al; Paediatric Rheumatology International Trials Organisation. Definition and Validation of the American College of Rheumatology 2021 Juvenile Arthritis Disease Activity Score Cutoffs for Disease Activity States in Juvenile Idiopathic Arthritis. *Arthritis Rheumatol* 2021;73(11):1966–1975.
25. Petty RE, Southwood TR, Manners P, et al; International League of Associations for Rheumatology. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol* 2004;31(2):390–392.
26. Ravelli A, Minoia F, Davi S, et al; Paediatric Rheumatology International Trials Organisation; Childhood Arthritis and Rheumatology Research Alliance; Pediatric Rheumatology Collaborative Study Group; Histiocyte Society. 2016 Classification Criteria for Macrophage Activation Syndrome Complicating Systemic Juvenile Idiopathic Arthritis: a European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. *Arthritis Rheumatol* 2016;68(3):566–576.
27. Metz CE. Basic principles of ROC analysis. *Semin Nucl Med* 1978;8(4):283–298.
28. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982;143(1):29–36.
29. Wallace CA, Giannini EH, Huang B, et al; Childhood Arthritis Rheumatology Research Alliance; Pediatric Rheumatology Collaborative Study Group; Paediatric Rheumatology International Trials Organisation. American College of Rheumatology provisional criteria for defining clinical inactive disease in select categories of juvenile idiopathic arthritis. *Arthritis Care Res (Hoboken)* 2011;63(7):929–936.
30. Magni-Manzoni S, Ruperto N, Pistorio A, et al. Development and validation of a preliminary definition of minimal disease activity in patients with juvenile idiopathic arthritis. *Arthritis Rheum* 2008;59(8):1120–1127.
31. Shoop-Worrall SJW, Verstappen SMM, Baildam E, et al. How common is clinically inactive disease in a prospective cohort of patients with juvenile idiopathic arthritis? The importance of definition. *Ann Rheum Dis* 2017;76(8):1381–1388.
32. Alongi A, Giancane G, Naddei R, et al; Pediatric Rheumatology International Trials Organization (PRINTO). Drivers of non-zero physician global scores during periods of inactive disease in juvenile idiopathic arthritis. *RMD Open* 2022;8(1):e002042.
33. Gohar F, Kessel C, Lavric M, et al. Review of biomarkers in systemic juvenile idiopathic arthritis: helpful tools or just playing tricks? *Arthritis Res Ther* 2016;18(1):163.