Defining criteria for disease activity states in systemic juvenile idiopathic arthritis based on the systemic Juvenile Arthritis Disease Activity Score

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Defining sJADAS cutoffs
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Title

Defining criteria for disease activity states in systemic juvenile idiopathic arthritis based on the systemic Juvenile Arthritis Disease Activity Score

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Key words

Pediatric rheumatology, juvenile idiopathic arthritis, systemic arthritis, Still's disease, composite disease activity score, disease activity, outcome measures

Objective: 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 (MiDA), moderate disease activity (MoDA), and high disease activity (HDA) in children with systemic juvenile idiopathic arthritis (sJIA), based on subjective disease state assessment by the treating pediatric rheumatologist.

Methods: The cutoffs 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, 6 methods were applied to identify the cutoffs: mapping, calculation of percentiles of cumulative score distribution, Youden index, 90% specificity, maximum agreement, and ROC curve analysis. Sixty percent of the patients were assigned to the

definition cohort and 40% to the validation cohort. Cutoff validation was conducted by assessing discriminative ability.

Results: The sJADAS10 cutoffs that separated ID from MiDA, MiDA from MoDA, and MoDA from HDA were ≤ 2.9, ≤ 10, and > 20.6. The cutoffs discriminated strongly among different levels of pain, between patients with or without morning stiffness, and between patients whose parents judged their disease status as remission or persistent activity/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 5-15% of all children diagnosed with JIA in Western countries, but is distinctly more prevalent in Southeast Asia, with reported frequencies higher than 30% in India, Thailand and Japan (1). It stands apart from the other categories of JIA, owing to the association of arthritis with prominent extra-articular manifestations, 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 (2,3) . Due to the emerging evidence that there are patients who possess the same clinical and biological systemic features observed in sJIA but never develop arthritis, new classification criteria that do not require the presence of arthritis have been proposed (4). Children with sJIA are uniquely susceptible to developing potentially life-threatening complications, namely macrophage activation syndrome (5) and inflammatory lung disease (6,7). Systemic JIA is regarded as the pediatric counterpart of adult-onset Still's disease (8–10).

Systemic JIA is considered the most severe form of childhood arthritis and 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 as 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, as achievement or persistence of inactive disease in JIA has been associated with better long-term outlook (11,12).

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 (13-19). Recently, a version specific to sJIA, named systemic JADAS (sJADAS), has been developed and validated (20). This tool includes, besides the four components of the JADAS (physician's global assessment of overall disease activity, PhGA; parent's/patient's global assessment of child's wellbeing, PaGA; count of joints with active disease; and an acute phase reactant), a fifth item aimed to quantify the activity of systemic manifestations, called modified Systemic Manifestation Score (mSMS).

To facilitate interpretation of scores obtained with sJADAS calculation, criteria (i.e., 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 (21–24).

This study was undertaken to determine and validate cutoff values in the sJADAS that distinguish the states of inactive disease (ID), minimal disease activity (MiDA), 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 (20) combines the following five key measures of disease activity in sJIA: 1) PhGA, measured on a 21-point 0-10 numerical rating scale (NRS) (where 0 = no activity and 10 maximum activity); 2) PaGA, measured on a 21-point 0-10 NRS (where 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); 4) ESR or CRP, both normalized to a 0-10 scale; 5) the mSMS, which includes the following seven clinical and/or laboratory features: (i) fever = 1 point if >37.5–38°C, 2 points if >38–39°C, 3 points if >39–40°C, 4 points if >40°C; (ii) evanescent erythematous rash = 1 point; (iii) generalized lymphadenopathy (enlargement of > 3 lymph node stations) = 1 point; (iv) hepatomegaly and/or splenomegaly = 1 point; (v) serositis (pleuritis, pericarditis or peritonitis) = 1 point; (vi) anemia (hemoglobin <9 g/dl) = 1 point; (vii) platelet count >600×10^9/l or ferritin >500 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, where 0 = absence of systemic manifestations and 10 = maximum activity of systemic manifestations.

Among the different versions of the original JADAS, the one that includes the 10-joint reduced count (i.e. JADAS10) is preferred by most investigators as it is simpler and equally 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 0-10 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

(20). Participating centers were asked to enroll all consecutive patients seen after the study start who had "definite" sJIA (i.e. a disease that met the ILAR criteria for sJIA (25)) or "probable"/"possible" sJIA (i.e. a febrile disease that presented with the classical extra-articular features of sJIA, but lacked overt arthritis). Patients with "probable"/"possible" sJIA would meet the newly proposed criteria for sJIA (4). Each patient could be enrolled at any of the following four disease activity states: ID, MiDA, 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 (20) were used for one specific validation analysis (see below).

Exclusion criteria included autoinflammatory illnesses, other febrile rheumatic disorders (e.g. Kawasaki disease), and febrile disorders resembling sJIA, but with known etiology. Patients with overt macrophage activation syndrome (26) or inflammatory lung disease (6,7) were also excluded. Patient enrolment 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, MiDA, MoDA, and 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.

Prior to the study visit, a parent was asked to rate the intensity of child's pain on a 21-point 0-10 NRS scale (where 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/flare, and to declare his/her satisfaction or non-satisfaction with current illness outcome.

Study data were collected in a standardized case report form and entered in an electronic database at the coordinating center (the Istituto Giannina Gaslini of 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) (21-24) was adapted for the present study. The following six methods were used to identify cutoffs in the sJADAS10 to distinguish the states of ID, MiDA, MoDA, and HDA in sJIA: mapping, calculation of percentiles of cumulative score distribution, Youden index, 90% specificity, agreement and receiver operating characteristic (ROC) curve drawing.

Mapping. For definition of the cutoff separating the states of ID and MiDA, 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 MiDA and MoDA, values below the 75th percentile of the sJADAS10 in patients judged by their treating physician as having ID or MiDA 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 75thpercentile 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 ID or MiDA, and patients with sJADAS10 values greater than the 75th percentile were considered HDA. This way of calculating the cutoffs has the advantage of being independent of treating physician's judgement.

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 = maxc = (Sens + Spc − 1) , where maxc is the maximally effective cutoff, Sens is the cutoff with the maximum sensitivity, and Spc 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 (27,28). 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 MiDA, the first group comprised patients judged by the treating physician as having ID 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 treating 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.

Evaluation of agreement. 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, MiDA, MoDA, or HDA) were considered as gold standard and evaluated in terms of observed agreement and Cohen's k concordance index.

Evaluation of ROC curve. This analysis was made using the classic method described by Metz in 1978 and by Hanley in 1982 (27,28) 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) between patients with different health states as assessed by their parents; 2) between patients meeting or not meeting the 2011 ACR provisional criteria for defining clinical inactive disease (CID) in JIA (hereinafter defined as Wallace criteria for CID) (29) and the preliminary definition of MiDA in JIA (hereinafter defined as Magni-Manzoni criteria for MiDA) (30); and 3) between patients evaluated at baseline visit in the previous study that led to develop and validate the sJADAS (20).

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 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 frequency 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 MiDA. We calculated the proportion of patients with ID, MiDA, 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 MiDA were only met by patients with sJADAS10-based ID or MiDA.

Ability to discriminate between patients at baseline visit in the sJADAS validation study (20). 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.

Quantitative measures were compared by the Kruskal-Wallis test. Percentages were compared by the chi-square test, or by the Fisher's Exact test in case of expected frequencies <5. All statistical test were two-sided, the alpha error was set at 0.05 and the software "R" (version 4.2.3) and Stata (release 17, College Station, TX, USA) 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/possible sJIA, and 22 patients were assessed in more than one

disease activity state. Owing to their low number and for sake of simplicity, patients with probable/possible sJIA were combined with those with definite sJIA; furthermore, the 22 visits made in the same patient in a different disease activity state were considered as referred 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 (1). The age at disease onset and at study visit was comparable across patients categorized in the different disease activity states, whereas the disease duration 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/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 MiDA, 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 MiDA, 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 MiDA/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).

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 through HDA (Figures 1 and 2). Conversely, the percentage of parents who reported being satisfied with current disease outcome or described their child's disease status as remission decreased progressively from ID through HDA (Figure 3 and Supplementary Figure S2).

Ability to discriminate between 2011 Wallace criteria for CID and Magni-Manzoni criteria for MiDA. Only 97 of the 152 (63.8%) patients who were classified as ID by the sJADAS met the 2011 Wallace criteria for CID (29) (Supplementary Table S5). However, only 7 of the 235 (3%) patients who did not have ID by the sJADAS met the Wallace criteria for CID

(Supplementary Table S6). The reasons that prevented the 55 patients with sJADAS ID from meeting the CID definition was a PhGA > 0 (n = 31), an elevated acute phase reactant (n = 29), and/or a count of active joints > 0 (n = 3) (Supplementary Figure S3). The reason that prevented all the 7 patients with met CID definition from meeting sJADAS ID was a PaGA ≥ 3 (range 3—7) (Supplementary Table S7). A better concordance was seen between Magni-Manzoni criteria for MiDA (30) and sJADAS-based criteria for MiDA (Supplementary Table S5).

Ability to discriminate between patients at baseline visit in the sJADAS validation study (20). At baseline visit of the present study, no patients met the sJADAS-based criteria for ID or MiDA, whereas a sizeable proportion of patients had HDA (Supplementary Figure S4).

Discussion

In this study, we determined the cutoffs in the sJADAS10 that correspond to the states of ID, MiDA, 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 standardization of assessments and minimize the impact of variability in perception of disease activity between physicians with diverse expertise, the assessors were provided with background information on the definition of the various disease states. The widening of enrolment to patients with a febrile disease that 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 (4) .

For the definition 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 (21–24). The selected cutoffs were those yielded by the ninety percent fixed specificity method for separation of ID from MiDA and of MiDA 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 MiDA had, beside 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 as having ID or MiDA patients whose disease was actually active and, thus, could deserve an aggressive therapy, and to minimize

the rate of misclassification of patients with MiDA or MoDA as having HDA, thus avoiding overtreatment. The good performance of the cutoffs was 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 between different health states based on the perception of parents living in different regions of the world. The cutoffs for ID and MiDA 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 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 illness outcome. The level of pain was lowest in patients who met the ID cutoffs and proportionally greater in patients who were in MiDA, MoDA, and HDA.

The cutoffs revealed only fair agreement with the Wallace criteria for CID (29) as around one third of the patients who had ID by 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 zero, 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 Wallace CID definition and JADAS ID criteria through an incongruous inflating effect on the JADAS, especially in the presence of persistent pain symptoms (31). The reason that prevented patients who met Wallace CID definition from meeting sJADAS ID was, indeed, a PaGA above the sJADAS ID threshold in all observed instances, although this disparity was recorded in only 7 (3%) of the patients. That the PhGA was more frequently responsible than the count of active joints for preventing

patients with sJADAS 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 who they find not to have active joints (32). Concordance was better between the sJADAS-based criteria for MiDA and the Magni-Manzoni criteria for MiDA (30), which were developed using the therapeutic decision made by the caring physician as 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, when patients were candidate to receive an aggressive therapeutic intervention. This finding suggests that the sJADAS10-based HDA cutoff is suitable to select patients for enrolment 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 perception of disease activity may vary between physicians practicing in different regions or with diverse expertise and treatment availability. However, 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. Nevertheless, the potential impact of discrepant perception 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 fashion for non-systemic forms of JIA. Due to the lack of longitudinal datasets 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 (33). 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 perception 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 strong ability to discriminate between disease activity states defined subjectively by the parents as well as between different levels of pain or presence or absence of morning stiffness. Furthermore, they corresponded well with established criteria for CID and MiDA 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.

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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 no. (%)	75 (50.0)	29 (38.7)	39 (44.8)	37 (42.0)
Female, no. (%)	75 (50.0)	46 (61.3)	48 (55.2)	51 (58.0)
Age at onset, years	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, years	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, years	3.5 (1.3-7.1)	3.4 (1-7)	3.3 (0.3-8)	0.6 (0.2-4.4)
Clinical outcome measures				
Physician global assessment[£]	0 (0-0)	1.5 (1-2.5)	6 (4-7)	8.5 (7.9-9)
Parent global assessment[£]	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[§]	0.5 (0-1.5)	4 (1.5-7.9)	20.4 (14.9-25.2)	31 (26.6-35.8)
Systemic manifestations				
Fever[&], no. (%)	0 (0)	0 (0)	39 (44.8)	82 (93.2)
Rash, no. (%)	0 (0)	5 (6.7)	21 (24.1)	47 (53.4)
Hepatomegaly, no. (%)	0 (0)	1 (1.3)	9 (10.3)	29 (33)
Splenomegaly, no. (%)	0 (0)	2 (2.7)	9 (10.3)	20 (22.7)
GLA, no. (%)	1 (0.7)	2 (2.7)	6 (6.9)	28 (31.8)
Serositis, no. (%)	0 (0)	0 (0)	6 (6.9)	10 (11.4)
Laboratory values				
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, $\times 10^9$/l	6.9 (5.4-8.4)	8.4 (7-10.4)	9.8 (7-15)	12.8 (8.9-17.8)
Neutrophil count, $\times 10^9$/l	3.1 (2.3-4.3)	4.2 (3-7)	5.9 (3.8-10.8)	8.3 (5-13.3)
Platelet count, $\times 10^9$/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 (233-1875)
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)

*sJIA = systemic juvenile idiopathic arthritis; sJADAS = systemic juvenile arthritis disease activity score; GLA = generalized lymphadenopathy; ESR = erythrocyte sedimentation rate. Values are the median (1st-3rd quartiles), unless otherwise indicated. [£]Measured on a 21-point 0-10 numerical rating scale scale, where 0 = best and 10 = worst. [§]Score range from 0 = no activity to 50 = maximum activity. [&]Body temperature > 37.5 °C in the 24 hours before the visit. All comparisons were significant (P<0.001) except for sex (P=0.36) and age at onset (P=0.15). The age at visit was significantly different among the 4 groups (P=0.015).

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 (75th / 25th percentile)£**	**Youden Index**	**90 % fixed specificity**
ID to MiDA	≤ 1.8 (75.3/92.5)	≤ 3 (89.4/89.7)	≤ 2.9 (85.9/91.8)
MiDA to MoDA	≤ 3.5 (75.2/97.2)	≤ 12 (98.4/88.7)	≤ 10 (95.2/91.5)
MoDA to HDA§	> 25.58 (75/92.7)	> 20.6 (94.2/85.5)	> 24.3 (82.7/90.5)
	Agreement (Cohen's kappa)	**25th/40th/75th percentile§**	**ROC curve**
ID to MiDA	≤ 3 (89.4/89.7)	≤ 1 (67.1/93.8)	≤ 3 (89.4/89.7)
MiDA to MoDA	≤ 12 (98.4/88.7)	≤ 3.5 (75.2/97.2)	≤ 12 (98.4/88.7)
MoDA to HDA§	>24.3 (82.7/90.5)	≥ 24.8 (80.8/91.1)	> 20.6 (94.2/85.5)

*sJADAS10 = systemic Juvenile Disease Activity Score 10; ROC=receiver operating characteristic; ID = inactive disease; MiDA = minimal disease activity; MoDA = moderate disease activity; HDA= high disease activity. Numbers in parentheses indicate sensitivity/specificity.

£The 75th percentile was applied for calculation of ID to MiDA and MiDA to MoDA cutoffs, whereas the 25th percentile was applied for calculation of MoDA to HDA cutoff.

§The 25th percentile was applied for calculation of ID to MiDA cutoff, whereas the 40th percentile was applied for calculation of MiDA to MoDA cuttoffs, and the 75th percentile was applied for calculation of MoDA to HDA cutoffs.

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 MiDA	≤ 2.9	90 % fixed specificity	85.9 / 91.8	Highest specificity with sensitivity > 85 %
MiDA 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 %

*sJADAS = systemic Juvenile Arthritis Disease Activity Score; sJIA = systemic juvenile idiopathic arthritis; ID = inactive disease; MiDA = minimal disease activity; MoDA = moderate disease activity; HDA = high disease activity.

Figure Legends

Figure 1. Comparison of the level of pain, measured on a 21-point 0-10 numerical rating scale, at visit among patients with sJADAS10-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 and 75th percentiles, dots within the boxes represent median values, and the lines outside the boxes represent the range. $P < 0.0001$ for comparison of disease states.

Figure 2. Percentage of patients who had morning stiffness of > 15 minutes among patients with sJADAS10-based inactive disease (ID), those with minimal disease activity (MiDA), those with moderate disease activity (MoDA), and those with high disease activity (HDA). $P < 0.0001$ for comparison of disease states.

Figure 3. Percentage of patients whose parents described the patient's symptom state as acceptable among patients with sJADAS10-based inactive disease (ID), those with minimal disease activity (MiDA), those with moderate disease activity (MoDA), and those with high disease activity (HDA). $P < 0.0001$ for comparison of disease states.