RHEUMATOLOGY

Rheumatology 2019;00:1–10
doi:10.1093/rheumatology/keaa240

Original article

Development and initial validation of a composite disease activity score for systemic juvenile idiopathic arthritis

Jessica Tibaldi[1,2], Angela Pistorio[3], Elena Aldera[2], Laura Puzone[2], Yasser El Miedany[4], Priyankar Pal [5], Prabhas Prasun Giri[5], Hriday De[5], Raju Khubchandani[6], Pallavi Pimpale Chavan[6], Soamarat Vilaiyuk[7], Butsabong Lerkvaleekul[7], Jutamas Yamsuwan[7], Tapas K. Sabui[8], Pragati Datta[8], Manuela Pardeo[9], Claudia Bracaglia[9], Sujata Sawhney[10], Sumidha Mittal[10], Waleed A. Hassan[11], Ghada Farouk Elderiny[12], Mohammed Hassan Abu-Zaid[13], Mervat Eissa [14], Flavio Sztajnbok[15], Fernanda C. das Neves Sztajnbok[16], Ricardo Russo[17], María Martha Katsicas[17], Rolando Cimaz[18], Edoardo Marrani[19], Ekaterina Alexeeva[20,21], Tatyana M. Dvoryakovskaya[20,21], Motasem O. Alsuweiti[22], Ra'ed M. Alzyoud[22], Mikhail Kostik[23], Irina Chikova[23], Francesca Minoia[24], Giovanni Filocamo[24], Yomna Farag[14], Hala Lotfy[14], Samah Ismail Nasef[25], Sulaiman M. Al-Mayouf[26], Maria Cristina Maggio[27], Claudia Saad Magalhaes[28], Romina Gallizzi[29], Giovanni Conti[30], Masaki Shimizu [31], Adele Civino[32], Enrico Felici[33], Gabriella Giancane[1,2], Nicolino Ruperto [1], Alessandro Consolaro[1,2] and Angelo Ravelli[1,2,21]

[1]UOC Clinica Pediatrica e Reumatologia, IRCCS Istituto Giannina Gaslini, Genoa, Italy, [2]Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e Scienze Materno-Infantili (DiNOGMI), Università degli Studi di Genova, Genoa, Italy, [3]Dipartimento di Epidemiologia e Biostatistica, IRCCS Istituto Giannina Gaslini, Genoa, Italy, [4]Faculty of Medicine, Ain Shams University, Cairo, Egypt, [5]Pediatric Rheumatology Division, Institute of Child Health, Kolkata, India, [6]Section of Pediatric Rheumatology, SRCC Children's Hospital, Mumbai, India, [7]Rheumatology Division, Pediatric Department, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, [8]Pediatric Rheumatology Clinic, R G Kar Medical College, Kolkata, India, [9]Division of Rheumatology, IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy, [10]Division of Pediatric Rheumatology, Institute of Child Health, Sir Ganga Ram Hospital, New Delhi, India, [11]Faculty of Medicine, Benha University, Benha, Egypt, [12]Faculty of Medicine, Alexandria University, Alexandria, Egypt, [13]Faculty of Medicine, Tanta University, Tanta, Egypt, [14]Faculty of Medicine, Cairo University, Cairo, Egypt, [15]Pediatric Rheumatology Division, Adolescent Health Care Unit, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil, [16]Department of Internal Medicine, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil, [17]Servicio de Inmunología y Reumatología, Hospital de Pediatría Garrahan, Buenos Aires, Argentina, [18]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy, [19]Division of Rheumatology, University Hospital Meyer, Florence, Italy, [20]Rheumatology Division, National Medical Research Center of Children's Health, Moscow, Russian Federation, [21]Sechenov First Moscow State Medical University, Moscow, Russian Federation, [22]Department of Immunology, Rheumatology and Allergy, Queen Rania Children's Hospital, Amman, Jordan, [23]Saint-Petersburg State Pediatric Medical University, Saint-Petersburg, Russian Federation, [24]UOC Pediatria a Media Intensità di Cure, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, [25]Rheumatology Department, Faculty of Medicine, Suez Canal University, Ismailia, Egypt, [26]Department of Pediatrics, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia, [27]Dipartimento Promise G. D'Alessandro, Università degli Studi di Palermo, Palermo, Italy, [28]Pediatric Department, Hospital das Clínicas - Botucatu Medicine University, UNESP, Botucatu, Brazil, [29]UOC Pediatria, Servizio di Immuno-Reumatologia Pediatrica, Azienda Ospedaliera Universitaria Gaetano Martino Messina, Messina, Italy, [30]UO Nefrologia e Reumatologia Pediatrica, Azienda Ospedaliera Universitaria Gaetano Martino, Messina, Italy, [31]Department of Pediatrics, School of Medicine, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kanazawa, Japan, [32]Pediatric Unit, Ospedale Vito Fazzi, Lecce, Italy and [33]Pediatric Unit, AON SS Antonio e Biagio e Cesare Arrigo Children's Hospital, Alessandria, Italy

Submitted 31 December 2019; accepted 6 April 2020

Correspondence to: Angelo Ravelli, Clinica Pediatrica e Reumatologia, IRCCS Istituto G. Gaslini, via G. Gaslini 5, 16147 Genoa, Italy. E-mail: angeloravelli@gaslini.org

CLINICAL SCIENCE

Abstract

Objective. To develop a composite disease activity score for systemic JIA (sJIA) and to provide preliminary evidence of its validity.

Methods. The systemic Juvenile Arthritis Disease Activity Score (sJADAS) was constructed by adding to the four items of the original JADAS a fifth item that aimed to quantify the activity of systemic features. Validation analyses were conducted on patients with definite or probable/possible sJIA enrolled at first visit or at the time of a flare, who had active systemic manifestations, which should include fever. Patients were reassessed 2 weeks to 3 months after baseline. Three versions were examined, including ESR, CRP or no acute-phase reactant.

Results. A total of 163 patients were included at 30 centres in 10 countries. The sJADAS was found to be feasible and to possess face and content validity, good construct validity, satisfactory internal consistency (Cronbach's alpha 0.64–0.65), fair ability to discriminate between patients with different disease activity states and between those whose parents were satisfied or not satisfied with illness outcome ($P < 0.0001$ for both), and strong responsiveness to change over time (standardized response mean 2.04–2.58). Overall, these properties were found to be better than those of the original JADAS and of DAS for RA and of Puchot score for adult-onset Still's disease.

Conclusion. The sJADAS showed good measurement properties and is therefore a valid instrument for the assessment of disease activity in children with sJIA. The performance of the new tool should be further examined in other patient cohorts that are evaluated prospectively.

Key words: systemic juvenile idiopathic arthritis, Still's disease, composite disease activity score, outcome measures, disease activity, clinical assessment, pediatric rheumatology

Rheumatology key messages

- No validated global disease activity tool for systemic JIA exists.
- We developed and validated the first composite disease activity score for systemic JIA.
- The new tool will increase the precision of disease activity assessment for systemic JIA.

Introduction

Systemic JIA (sJIA) accounts for 5–15% of all children with chronic arthritis seen in Europe and North America, but is much more common in southeast Asia, with a reported frequency in India, Thailand and Japan as high as 25–50% [1, 2]. It is quite distinct from the other categories of JIA, owing to the association of arthritis with particular extraarticular manifestations, which include high-spiking fever, erythematous macular rash, generalized lymphadenopathy, hepatosplenomegaly and serositis [3, 4]. Typical laboratory features include microcytic anaemia, leucocytosis, thrombocytosis, elevated immunoglobulins, increased ESR, CRP and fibrinogen, and hypoalbuminemia. Children with sJIA are uniquely susceptible to developing a potentially life-threatening hyperinflammatory complication known as macrophage activation syndrome [5]. There is nowadays wide agreement that sJIA and adult-onset Still's disease constitute the same disease occurring at different ages [6–8].

Regular measurement of level of disease activity in children with sJIA is important in monitoring the disease course over time and in treat-to-target strategies [9]. However, clinical instruments specifically validated for use in sJIA are lacking. Criteria for clinically inactive disease [10, 11] and minimal disease activity [12] are suitable for use in sJIA. However, they have been designed to define a particular disease activity state and do not allow quantitative estimation.

In the last decade, the Juvenile Arthritis Disease Activity Score (JADAS) has gained increasing popularity for the assessment of disease activity in children with JIA [13–15]. However, although the JADAS has been used in studies of sJIA [16], its validation analysis was conducted only in children with oligoarthritis and polyarthritis, including sJIA without extraarticular manifestations, but not in children with sJIA and active systemic features [13].

Because systemic symptoms have a major impact on a child's well-being and play a key role in driving therapeutic decisions, any instrument used to quantify the level of disease activity in sJIA must incorporate their assessment [17]. In the past, systemic feature scores and a disease activity core set have been devised [18–20], but none has been widely embraced.

Against this background, the primary purpose of the present study was to develop a new version of the JADAS specific to sJIA, named systemic JADAS (sJADAS), and to provide preliminary evidence of its validity.

Methods

Development of the sJADAS

The sJADAS was devised by a panel of five pediatric rheumatologists with 2 to >30 years of experience in clinical care and assessment of children with sJIA (J.T., G.G., A.C., N.R. and A.R.). All investigators agreed that although the original JADAS was suitable to measure the level of disease activity in sJIA, it lacked a component aimed at quantifying the burden of extra-articular manifestations. It was therefore decided to construct the new score by adding to the four items of the JADAS a fifth item aimed at measuring the activity of systemic disease. After the analysis of the published tools aimed to quantify systemic symptoms in sJIA [18–21], consensus was reached on the choice of the Systemic Manifestation Score (SMS) [21], which was felt to be the most suitable.

The SMS includes the following seven clinical and/or laboratory features: (i) fever = 1 point if 37–38°C, 2 points if >38–39°C, 3 points if >39–40°C, 4 points if >40°C; (ii) rash = 1 point; (iii) generalized lymphadenopathy = 1 point; (iv) hepatomegaly and/or splenomegaly = 1 point; (v) serositis = 1 point; (vi) anaemia (haemoglobin <9 g/dl) = 1 point; (vii) platelet count >600 × 10^9/l or ferritin >500 ng/ml = 1 point. Fever is assigned a greater weight owing to its major impact on a child's well-being and importance in driving treatment decisions. Fever was the sole extra-articular feature added to the six core set variables in the adaptation of the ACR Pediatric response criteria used in clinical trials on biologic medications in sIJA [22, 23, 24]. Furthermore, resolution of fever was recently set as the primary short-term therapeutic target in sJIA [9]. However, because we realized that a cut-off for fever at 37°C may be regarded as too low as the presence of fever is commonly defined as a body temperature ≥37.5°C, we modified the original SMS score by giving 1 point to a temperature range from 37.5 to 38°C instead of from 37 to 38°C. Fever was defined as the highest temperature recorded in the 24 h before the visit. The temperature should have been measured with a thermometer by the parents in the mouth, ear, armpit, rectum or forehead. We selected the maximum temperature in the past 24 h, because we thought that it was most closely related to the other systemic manifestations, especially rash, at the time of the visit. For the sake of clarity, we further modified the SMS by adding the definitions for generalized lymphadenopathy and serositis. We also warned that in the assessment of fever its possible pharmacologic suppression should be taken into account. The modified version of the SMS (mSMS), which is shown in Table 1, ranges from 0 to 10, where 0 = absence of systemic manifestations and 10 = maximum activity of systemic manifestations.

The final sJADAS was made up of the following five items: (i) physician global assessment of overall disease activity, measured on a 10-cm visual analogue scale (0 = no activity; 10 = maximum activity); (ii) parent/patient global assessment of well-being, measured on a 10-cm visual analogue scale (0 = very well; 10 = very poor); (iii) count of active joints in 10, 27 or 71 joints, depending on the version (i.e. sJADAS10, sJADAS27 and sJADAS71, respectively); (iv) ESR or CRP level, both normalized to a 0–10 scale, as reported [13, 25]; and (v) the mSMS, composed and scored as above. The sJADAS is calculated as the simple linear sum of the scores of its five components, which yields a global score of 0–67, 0–111 and 0–50, respectively, for the sJADAS27, sJADAS71 and sJADAS10.

Table 1 Modified Systemic Manifestation Score

Clinical or laboratory feature	Points
Fever[a]	
37.5–38°C	1
>38–39°C	2
>39–40°C	3
>40°C	4
Evanescent erythematous rash	1
Generalized lymphadenopathy (enlargement of >3 lymph node stations)	1
Hepatomegaly and/or splenomegaly	1
Serositis (pleuritis, pericarditis or peritonitis)	1
Anaemia (haemoglobin <9 g/dl)	1
Platelet count >600 × 10^9/l or ferritin >500 ng/ml	1

[a]Fever is defined as the maximum temperature either in the past 24 h, 3 days or week. In the assessment of fever, the possible pharmacologic suppression of temperature by paracetamol, NSAIDs or glucocorticoids should be taken into account. Modified with permission from [21].

The version used in validation analyses was the sJADAS10. The composition and score ranges of the sJADAS10, the original JADAS10 [13], the clinical JADAS10 (cJADAS10) [26, 27], and of two composite scores used in adult RA, the DAS in 28 joints (DAS28) [28] and the Clinical Disease Activity Index [28], are shown in Table 2.

Data collection

Participation in the study was proposed to 27 centres of the Italian Pediatric Rheumatology Study Group and to 16 international paediatric rheumatology centres located in geographic regions with a high prevalence of sJIA. Participating centres were asked to enroll consecutive patients who had new-onset 'definite' sJIA (i.e. a disease that met the ILAR criteria for sJIA [29]) or 'probable/possible' JIA (i.e. a febrile disease that presented with the classical extra-articular features of systemic JIA, but lacked overt arthritis). All patients would meet the recently proposed new criteria for sJIA [30]. Patients with definite sJIA could also be enrolled at the time of a disease flare. All patients should have active systemic manifestations, comprising fever.

Exclusion criteria included monogenic autoinflammatory illnesses and other febrile rheumatic disorders (e.g.

Table 2 Composition and theoretical range of the composite disease activity scores tested in the study

	sJADAS10	JADAS10	cJADAS10	DAS28	CDAI
Physician global assessment	0–10 cm VAS	0–10 cm VAS	0–10 cm VAS	–	0–10 cm VAS
Parent/patient global assessment	0–10 cm VAS	0–10 cm VAS	0–10 cm VAS	0–1.40 mm VAS	0–10 cm VAS
Active joint count	Simple, 0–10 joints[a]	Simple, 0–10 joints[a]	Simple, 0–10 joints[a]	–	–
Swollen joint count (range)	–	–	–	28 joints, square root-transformed (0–1.48)	Simple, 0–28 joints
Tender joint count (range)	–	–	–	28 joints, square root-transformed (0–2.96)	Simple, 0–28 joints
Acute-phase reactant (range)	Normalized ESR[b] or CRP[c] (0–10)	Normalized ESR (0–10)	–	Log-transformed ESR (0.49–3.22)	–
Systemic manifestation score (range)[d]	0–10	–	–	–	–
Score range	0–50	0–40	0–30	0.49–9.07	0–76

[a]Up to 10 joints, irrespective of their type, censored at 10. [b]According to the formula: (value in mm/h − 20)/10, where values <20 mm/h are converted to 0, and values >120 mm/h are converted to 120. [c]According to the formula (value in mg/l − 10)/10, where values <10 mg/l are converted to 10, and values >110 mg/l are converted to 110. [d]See text for composition and score calculation. sJADAS10: systemic Juvenile Arthritis Disease Activity Score in 10 joints; JADAS10: JADAS in 10 joints; cJADAS10: clinical JADAS in 10 joints; DAS28: DAS in 28 joints; CDAI: Clinical Disease Activity Index; VAS: visual analogue scale.

Kawasaki disease). Patients with sJIA with active arthritis but lacking systemic manifestations were excluded. Patient enrollment was started on 1 February 2017 and closed on 31 December 2018. Ethical approval was obtained in all countries involved in the study.

Clinical assessments

At study entry, study investigators were asked to register patients' demographic data and to perform all assessments required to calculate the composite disease activity scores. Additional evaluations included the physician subjective assessment of disease state as inactive disease or low, moderate or high disease activity, and the assessment of disease course at second visit as improved, stable or worsened. Study investigators were instructed to base these assessments on their subjective perception of the disease status and course. A brief definition of each disease state was provided as reference. Prior to the study visit, a parent was asked to complete the parent proxy-reported national-language version of the Juvenile Arthritis Multidimensional Assessment Report [31], which includes assessment of physical function, health-related quality of life and satisfaction with illness outcome. Investigators were asked to repeat all baseline assessments at the subsequent visit, after 2 weeks to 3 months.

Study data were collected in a standardized case report form and entered in an electronic database at the coordinating centre (the Istituto Giannina Gaslini of Genoa, Italy).

Validation procedures

Validation of the sJADAS10 was conducted following standard procedures [32–35]. Feasibility or practicality was determined by addressing the issues of brevity, simplicity and easy scoring. Face and content validity were established by determining that all items: (i) referred to relevant aspects of the construct to be measured (i.e. sJIA disease activity); (ii) were relevant to a population of patients with sJIA and active systemic manifestations; (iii) had good discriminative and evaluative properties; and (iv) comprehensively reflected, altogether, the construct to be measured.

Three versions of the sJADAS10 were tested in validation analyses: a version including the ESR (sJADAS10-ESR), a version including the CRP (sJADAS10-CRP) and a version lacking the acute-phase reactant (sJADAS10-no APR). Furthermore, the performance of the sJADAS was compared with that of JADAS10 [13], cJADAS10 [26, 27], DAS28 [28], Clinical Disease Activity Index [29] and Pouchot score for adult-onset Still's disease [36]. The latter score assigns 1 point to each of the following 12 manifestations: fever, typical rash, pleuritis, pneumonia, pericarditis, hepatomegaly or abnormal liver function tests, splenomegaly, lymphadenopathy, leucocytosis $\geq$15 000/mm^3, sore throat, myalgia and abdominal pain. The Pouchot score was tested both individually and as substitute of the mSMS in the sJADAS-ESR (the so-called sJADAS10-Pouchot).

Construct validity was assessed by examining whether the sJADAS is related to other clinical outcome

measures not included in the score in a manner consistent with *a priori* prediction. Correlations were computed on score changes between baseline and second visit, using Spearman's rank statistics and were considered high if >0.7, moderate if 0.4–0.7 and low if <0.4 [37].

Internal consistency was assessed using Cronbach's alpha coefficient [38] and was defined as follows: <0.6 = poor, 0.6–0.64 = slight, 0.65–0.69 = fair, 0.7–0.79 = moderate, 0.8–0.89 = substantial and ≥0.9 = almost perfect [39]. The dimensional structure of the sJADAS10 was examined using exploratory factor analysis [40, 41], which can determine whether a scale is measuring more than one construct. It generates factor loadings, which are measurements of how strongly the variables in the scale are associated with its latent factor(s).

To evaluate whether the sJADAS10 can differentiate between patients with varying levels of disease activity, we compared its scores between patients grouped using physician subjective estimation of disease activity state (rated as inactive, low, moderate or high) and parent satisfaction with illness outcome [42]. It was expected that the sJADAS10 score was lower among patients judged by the physician in inactive disease or whose parents were satisfied with illness outcome. Comparison among groups was made by Mann–Whitney *U* test and Kruskall–Wallis test, as appropriate.

Responsiveness to change was assessed through the standardized response mean, calculated as the mean change in score divided by the S.D. of individuals' change in score from baseline to second visit. Threshold levels for standardized response mean were defined as follows: ≥0.2 = small, ≥0.5 = moderate and ≥0.80 = good [43].

All statistical tests were two sided; a *P*-value <0.05 was considered statistically significant. The statistical packages used were 'Statistica' (release 6.1, StatSoft, Tulsa, OK, USA), Stata release 9.2 (Stata Corporation, College Station, TX, USA), XLSTAT (version 1.02, Addinsoft, 2013) for Cronbach's alpha calculation, and R statistics (version 3.3.3) [The R foundation for Statistical Computing, Vienna, Austria (https://www.R-project.org/)].

Results

A total of 163 patients, whose demographic and clinical features at study entry (baseline) and at second visit are summarized in supplementary Table S1, available at *Rheumatology* online, were included in the study at 30 centres in 10 countries. The female-to-male ratio and age at disease onset were typical of sJIA [4]. The majority of patients had definite sJIA and more than half were enrolled at first observation at study centre. Thirty-nine patients who met the ILAR clinical criteria for sJIA, but had a disease duration at study entry of <6 weeks, which is a mandatory time frame for diagnosis of sJIA in the ILAR classification, were placed in the possible/probable sJIA category. The frequency of systemic symptoms was comparable between patients with definite and probable/possible sJIA (results not shown).

The values of clinical outcome measures, laboratory tests and composite disease activity scores at study entry and at second visit are shown in Table 3. As expected, the level of disease activity was high at baseline, and decreased markedly at second visit, as a result of therapeutic interventions performed between the two assessments. Table 4 reports the value or frequency of the individual items of the mSMS at study entry and second visit. All patients had fever by inclusion criteria and the median maximum temperature in the 24 h preceding baseline visit was 39°C.

Feasibility and face and content validity

All members of the study panel and all participating investigators agreed that the proposed tool possessed these properties.

Construct validity

Spearman's correlations between the sJADAS10 and the other composite DAS and the outcome measures not included in the scores, assessed on changes in values between baseline and second visit, are shown in Table 5. All correlations between sJADAS10 and parent-reported outcomes were in the moderate range (0.41–0.60) and were overall better for the sJADAS10-ESR than for the versions with CRP or without APR. sJADAS10-ESR correlations were comparable to those of JADAS10 (0.42–0.62) and cJADAS10 (0.38–0.57), but higher than those of adult composite scores (0.07–0.56), with the exception of similar correlations for the sJADAS10-Pouchot (0.46–0.60).

Internal consistency

Cronbach's alpha values for sJADAS10 were slight-to-fair (0.64–0.65) and marginally better than those for JADAS10 (0.60) and cJADAS10 (0.63) (see supplementary Table S2, available at *Rheumatology* online). Removal of all individual items of sJADAS10 one at a time decreased internal consistency, with the sole exception of ESR removal from sJADAS10-ESR, which increased Cronbach's alpha value (results not shown). Internal consistency of sJADAS10-ESR (0.64) was superior to that of the sJADAS10-Pouchot (0.55).

Factor analysis

Exploratory factor analysis showed that the sJADAS10 measured only one construct. Correlations between individual items and the latent factor were greater for physician global assessment, followed by parent global assessment and active joint count (see supplementary Table S3, available at *Rheumatology* online).

Discriminant validity

The sJADAS10 revealed strong ability to discriminate patients categorized subjectively in different disease

TABLE 3 Values of outcome measures and laboratory tests at study entry and at second visit*

	Baseline		Second visit	
	No.	Median (IQR)	No.	Median (IQR)
Physician global assessment of overall disease activity[a]	160	7.5 (6–9)	157	1 (0–3.5)
Parent global assessment of child's wellbeing[a]	159	7.5 (5–9)	157	2 (0–4)
Parent assessment of pain[a]	160	7.5 (5–9)	150	0.5 (0–3)
Physical function score[b]	159	13 (5–24)	154	0 (0–4)
HRQL PhH score[c]	151	9 (4–12)	148	2 (0–5)
HRQL PsH score[c]	151	4 (2–7)	148	2 (0–3)
No. swollen joints	161	3 (0–7)	157	0 (0–1)
No. tender joints	158	4 (1–11)	154	0 (0–1)
No. joints with limited range of motion	158	3 (1–8)	157	0 (0–0)
No active joints	161	4 (1–10)	157	0 (0–2)
White blood cell count, $\times 10^9$/l	161	15 (9.6–20)	161	11.3 (7.8–15)
Neutrophil count, $\times 10^9$/l	159	8.8 (4.9–14.2)	159	6.2 (4.0–9.0)
Haemoglobin, gm/dl	162	10.1 (8.9–11.1)	162	11.8 (10.6–12.8)
Platelet count, $\times 10^9$/l	161	468 (349–575)	161	354 (271–450)
Ferritin, ng/ml	152	874 (284–2956)	152	161 (60–330)
ESR, mm/h	160	65 (40–95)	160	18 (7–36)
CRP, mg/dl	153	13.9 (7.9–24.3)	153	1 (0.3–4.8)
Fibrinogen, g/l	98	518 (350–637)	98	264.5 (199–374)
JADAS10[d]	160	23.3 (17.3–28.5)	157	6 (1–10.5)
cJADAS10[e]	160	18.5 (13.3–24.3)	157	4 (0.5–9)
DAS28[f]	157	5 (3.9–6.1)	151	2.4 (1.7–3.3)
CDAI[g]	157	18.5 (14.0–28.0)	156	4.0 (0.5–9.5)
mSMS[h]	162	5 (4–6)	156	0 (0–2)
sJADAS10-ESR[i]	160	28.2 (22.6–34.9)	156	6.5 (1.8–12.3)
sJADAS10-CRP[i]	151	32.4 (27.2–39.0)	146	6.8 (2.0–8.6)
sJADAS10-no APR[i]	160	24.0 (18.8–30.0)	156	5.0 (1.3–11.0)
sJADAS-ESR-Pouchot[l]	157	26.4 (21.0–32.8)	156	6.5 (1.7–12.4)
Pouchot score[m]	159	3.0 (3.0–5.0)	156	1.0 (0.0–1.0)

No. refers with patients with the item available. [a]On a 0–10 visual analogue scale (0 = best; 10 = worst); [b]score ranges from 0 (no disability) to 30 (maximum disability); [c]score ranges 0–15, higher scores indicate worse HRQL; [d]score ranges from 0 to 40 (0 = no activity; 40 = maximum activity); [e]score ranges from 0 to 30 (0 = no activity; 30 = maximum activity); [f]score ranges from 0.49–9.07 (0.49 = no activity; 9.07 = maximum activity); [g]score ranges from 0 to 76 (0 = no activity; 76 = maximum activity); [h]score ranges from 0 to 10 (0 = no systemic activity; 10 = maximum systemic activity); [i]score ranges from 0 to 50 (0 = no activity; 50 = maximum activity); [j]score ranges from 0 to 52 (0 = no activity; 52 = maximum activity); [k]score ranges from 0 to 12 (0 = no activity; 12 = maximum activity). IQR: interquartile range; HRQL: health-related quality of life; PhH: physical Health; PsH: psychosocial health; JADAS: Juvenile Arthritis Disease Activity Score; cJADAS: clinical JADAS; DAS28: DAS in 28 joints; CDAI: Clinical Disease Activity Index; mSMS: modified Systemic Manifestation Score; sJADAS: systemic JADAS; sJADAS-ESR: sJADAS with ESR; sJADAS-CRP: sJADAS with CRP; sJADAS-no APR: sJADAS without acute-phase reactant; sJADAS-ESR-Pouchot: sJADAS with ESR and Pouchot score instead of mSMS.

activity states by the caring physician ($P < 0001$) (Fig. 1) and between patients whose parents were satisfied or not satisfied of illness outcome ($P < 0.0001$) (see supplementary Fig. S1, available at *Rheumatology* online).

Responsiveness to change

The standardized response mean values were good for all three versions of the sJADAS10 (2.04–2.58), although lower for the one without APR, in both the whole patient sample (2.04) and the patient subgroup judged as improved at second visit by the caring physician (2.18). Responsiveness of sJADAS10 was better than that of JADAS10 (2.06–2.17), cJADAS10 (1.81–1.89), adult composite scores (1.39–1.86) and sJADAS10-Pouchot (2.12–2.27) (see supplementary Table S4, available at *Rheumatology* online).

Discussion

We have described the development of a composite disease activity score specific to sJIA and provided preliminary evidence of its validity. The sJADAS combines the four disease activity measures included in the original JADAS with a fifth component, the mSMS, which is aimed at quantifying the activity of extra-articular symptoms. The score of the sJADAS results from the

arithmetic sum of the values of each individual component, which makes its calculation simple and quick.

Validation procedures were conducted on a multinational inception cohort, comprising a total of 163 patients enrolled by paediatric rheumatologists practicing in 10 countries. The study sample is likely representative of the entire spectrum of children with sJIA seen in paediatric rheumatology centres worldwide. At study entry, all patients had to have active disease with ongoing systemic manifestations, which should include fever. To evaluate the capacity of the tool to capture the change in disease activity over time, patients were reassessed at the subsequent visit, when disease activity was expected to be decreased as a result of therapeutic interventions prescribed at initial visit.

In validation analyses, the sJADAS was found to be feasible and to possess face and content validity, good construct validity, satisfactory internal consistency, appropriate dimensional structure, fair discriminative validity and strong responsiveness to clinically important change over time. By documenting these key measurement properties, we have demonstrated that the sJADAS is a valid tool for the assessment of disease activity in this patient population and is therefore applicable in both clinical and research settings. Overall, the performance of the sJADAS was superior to that of the original JADAS and of adult disease activity scores.

We tested three versions of the sJADAS, which included ESR or CRP, or lacked the APR. The sJADAS-ESR performed best in construct validity assessment, whereas the sJADAS-CRP revealed superior internal consistency and better responsiveness to change. In addition, CRP was better correlated than the ESR with latent factor in factor analysis and did not lead, as opposed to ESR, to a drop in Cronbach's alpha when removed from the instrument. Considering the overall performance in validation analyses, we would favour the use of the sJADAS10-CRP over the version with the ESR. Notably, the sJADAS version without APR showed satisfactory metrological properties, which suggests that it is potentially suited for use in routine clinical practice, when an APR is not obtained or is missing. Given the characteristics of patients enrolled, all of whom had fever, the sJADAS should be applied only in sJIA patients with fever or other active systemic manifestations. In patients who lack extra-articular features and have a polyarticular course of their disease, the traditional JADAS may be preferred.

Table 4 Value or frequency of individual components of mSMS at study entry and at second visit

	Baseline	Second visit
Median (IQR) highest temperature in the last 24 h, °C ($n = 157$)	39.0 (38.0–39.2)	36.8 (36.0–37.0)
No. (%) of patients with skin rash	118/161 (73.3)	7/156 (4.5)
No. (%) of patients with generalized lymphadenopathy	69/161 (42.9)	9/156 (5.8)
No. (%) of patients with hepatomegaly and/or splenomegaly	91/161 (56.5)	27/157 (17.2)
No. (%) of patients with serositis	24/161 (14.9)	3/155 (1.9)
No. (%) of patients with haemoglobin <9 g/dl	41/162 (25.3)	9/152 (5.9)
No. (%) of patients with platelet count $>600 \times 10^9$/l and/or ferritin >500 ng/ml	112/159 (70.4)	27/131 (20.6)

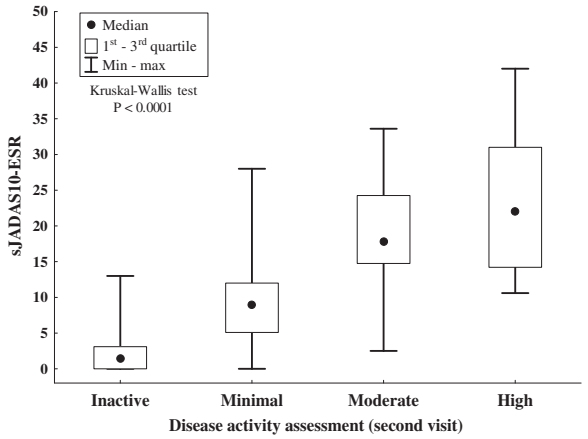
IQR: interquartile range.

Table 5 Spearman's correlation between composite scores and JIA outcome measures not included in the scores[a]

	ESR	CRP	Parent pain assessment	Physical function score	HRQL PhH score	HRQL PsH score
sJADAS10-ESR	–	0.28 ($n = 141$)	0.60 ($n = 146$)	0.53 ($n = 151$)	0.51 ($n = 141$)	0.43 ($n = 141$)
sJADAS10-CRP	0.23 ($n = 138$)	–	0.50 ($n = 134$)	0.44 ($n = 138$)	0.44 ($n = 130$)	0.43 ($n = 130$)
sJADAS10-no APR	0.16 ($n = 148$)	0.24 ($n = 141$)	0.57 ($n = 146$)	0.46 ($n = 151$)	0.49 ($n = 141$)	0.41 ($n = 141$)
JADAS10	–	0.29 ($n = 141$)	0.62 ($n = 147$)	0.55 ($n = 152$)	0.52 ($n = 142$)	0.42 ($n = 142$)
cJADAS10	0.12 ($n = 149$)	0.23 ($n = 141$)	0.57 ($n = 147$)	0.48 ($n = 152$)	0.47 ($n = 142$)	0.38 ($n = 142$)
DAS28	–	0.17 ($n = 136$)	0.54 ($n = 139$)	0.56 ($n = 144$)	0.47 ($n = 137$)	0.39 ($n = 137$)
CDAI	0.1 ($n = 145$)	0.17 ($n = 137$)	0.45 ($n = 143$)	0.50 ($n = 148$)	0.41 ($n = 140$)	0.23 ($n = 140$)
sJADAS-ESR-Pouchot	–	0.26 ($n = 138$)	0.60 ($n = 144$)	0.50 ($n = 149$)	0.52 ($n = 139$)	0.46 ($n = 139$)
Pouchot score	0.12 ($n = 147$)	0.15 ($n = 140$)	0.20 ($n = 146$)	0.07 ($n = 151$)	0.23 ($n = 139$)	0.33 ($n = 139$)

[a]Correlations have been assessed on the absolute change between baseline and second visit. HRQL: health-related quality of life; PhH: physical health; PsH: psychosocial health. sJADAS10: systemic Juvenile Arthritis Disease Activity Score in 10 joints; sJADAS-ESR: sJADAS with ESR; sJADAS-CRP: sJADAS with CRP; sJADAS-no APR: sJADAS without acute-phase reactant; JADAS10: JADAS in 10 joints; cJADAS10: clinical JADAS10; DAS28: DAS in 28 joints; CDAI: Clinical Disease Activity Index; sJADAS-ESR-Pouchot: sJADAS with ESR and Pouchot score instead of mSMS.

Fig. 1 Capacity of sJADAS10-ESR to discriminate between disease activity states



sJADAS10-ESR: systemic Juvenile Arthritis Disease Activity Score in 10 joints with ESR.

Our study has some caveats. We recognize that the new tool was developed by a restricted group of experts and, although agreed upon by a large group of international paediatric rheumatologists, was not derived from a formal Delphi survey. The choice of the mSMS to measure the activity of systemic manifestations was arbitrary and other published instruments [19–21] or another format of the tool could be more appropriate. Unfortunately, we could not compare the validity of the sJADAS with that of the core set of variables proposed by Limenis *et al.* [20], because our data did not allow the calculation of the number of fever and rash days in the past 2 weeks, which is needed to assess the fever and rash items. The value of the Limenis core set is, nevertheless, worth testing in future analyses. We acknowledge that the SMS was originally proposed as a tool to assess baseline predictors of anakinra treatment outcome [21] and was not designed for the assessment of treatment response, serial measurement of disease activity or estimation of a particular disease state. We also recognize that assessment of fever at intervals other than in the past 24 h, such as in the preceding 3 days of week, could be more reliable or meaningful. However, the mSMS values obtained using the maximum temperature in these time intervals were comparable to those yielded by the past 24 h (results not shown). The requirement for measurement of maximal body temperature in the 24 h prior to sJADAS assessment may not be practical for patients with established disease in the outpatient setting. It may be difficult for a family of a child with fever to repeatedly take and record the child's temperature throughout the night. That the cut-offs for laboratory tests were not data-driven, but based on expert consensus, could hinder their face validity. We did not evaluate the characteristics and behaviour of the sJADAS in patients who have a flare of systemic manifestations without the presence of fever (for example, rash). Due to the lack of long-term assessments, we could not investigate the capacity of the sJADAS to predict disease outcomes, such as continued activity, cumulative damage or functional disability. Our effort did not take into account the recent scientific evidence for biomarkers of immune activation and systemic inflammation in sJIA [44]. Although these biomarkers are still not available on a routine basis, they will likely be included in future tools for disease activity measurement.

In conclusion, we have devised a new composite disease activity score for sJIA, which is composed of the five key disease activity measures for this disease. This instrument is feasible and easily applicable in routine clinical practice, which should result in its widespread acceptance and use. In validation analyses, the sJADAS was found to possess good measurement properties, which indicates that it is applicable in both clinical and research settings, including clinical trials. The measurement performances of the sJADAS should be externally validated in other patient cohorts that are evaluated prospectively, including patients with adult-onset Still's disease. Another future key objective is to define the cut-offs in the score that correspond to the states of inactive disease and low, moderate and high disease activity. In line with the recent recommendations for the treat-to-target strategy in JIA [9], there is a need to aim at reaching the lowest possible sJADAS in sJIA, preferably in glucocorticoid-free patients.

Acknowledgements

The authors thank Dr Elisa Patrone, Genoa, Italy for her invaluable role in organizing the study, preparing the database and entering patient data. Permission for use of Childhood Health Assessment Questionnaire and Child Health Questionnaire derived-material is granted through the scientific cooperation of the copyright holder ICORE of Woodside CA and HealthActCHQ Inc. of Boston, MA, USA. All CHQ-related inquiries are directed to licensing@healthactchq.com.

Funding: No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

Disclosure statement: The authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* online

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