UNIVERSITY OF NAPLES FEDERICO II

PH.D. PROGRAM IN

CLINICAL AND EXPERIMENTAL MEDICINE

CURRICULUM IN TRANSLATIONAL PEDIATRIC SCIENCES

XXXV Cycle
(Years 2019-2022)

Chairman: Prof. Francesco Beguinot

PH.D. THESIS

Clinical outcome measures in juvenile idiopathic arthritis: toward a new disease activity score based on the parent/patient's perspective

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Chapter 1

Background and aims

The term juvenile idiopathic arthritis (JIA) encompasses all forms of arthritis that begin before the age of 16 years, persist for more than 6 weeks, and are of unknown cause. According to the International League of Associations for Rheumatology (ILAR) classification, seven categories of JIA are recognized based on features present in the first 6 months of illness (table 1) (1). JIA is the most common chronic rheumatic disease.

ILAR category	Frequency* (%)	Onset (age, years)	Sex ratio (F:M)	Inclusion criteria
Systemic arthritis	4-17	Throughout childhood	1:1	Arthritis in one or more joints with or preceded by fever of at least 2 weeks' duration that is documented to be daily for at least 3 days, and accompanied by one or more of the following: evanescent erythematous rash; generalized lymph node enlargement; hepatomegaly and/or splenomegaly; serositis.
Oligoarthritis	27-56	<6	4:1	Arthritis affecting one to 4 joints during the first 6 months of disease. Two subcategories are recognized: persistent oligoarthritis: affecting not more than 4 joints throughout the disease course; extended oligoarthritis: affecting a total of more than 4 joints after the first 6 months of disease.
RF-positive polyarthitis	2-7	9-12	9:1	Arthritis affecting 5 or more joints during the first 6 months of disease; 2 or more tests for RF at least 3 months apart during the first 6 months of disease are positive.
RF-negative polyarthritis	11-28	Biphasic distribution (2-4; 6-12)	3:1	Arthritis affecting 5 or more joints during the first 6 months of disease; a test for RF is negative.
Psoriatic arthritis	2-11	Biphasic distribution (2-4; 9-11)	2:1	Arthritis and psoriasis, or arthritis and at least 2 of the following: dactylitis, nail pitting or onycholysis, psoriasis in a first-degree relative.
Enthesitis-related arthritis	3-11	9-12	1:7	Arthritis and enthesitis, or arthritis or enthesitis with at least 2 of the following: the presence of or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain; the presence of HLA-B27 antigen; onset of arthritis in a male over 6 years of age; acute (symptomatic) anterior uveitis; history of ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's

		syndrome, or acute anterior uveitis in a first-degree relative.
Undifferentiated arthritis	11-21	Arthritis that fulfills criteria in no category or in 2 or more of the above categories.

Table 1: Frequency, age at onset, sex distribution, and inclusion criteria of the International League of Associations for Rheumatology (ILAR) categories of juvenile idiopathic arthritis (1, 2). *Reported frequencies refer to percentage of all juvenile idiopathic arthritis.

The etiology of JIA is unknown, although it is almost certainly multifactorial, and probably differs from one onset type to another. The pathogenetic process underneath JIA is chronic inflammation, in which both innate and adaptive immune systems play critical roles. In all categories of JIA, an autoimmune synovitis is sustained by cytokines produced by activated T cells and macrophages, leading to the classic signs of inflammation (swelling, pain, heat, loss of function) in the actively inflamed joints (3).

Management of JIA is based upon a combination of pharmacological interventions, physical and occupational therapy, and psychosocial sustenance (2, 3). Indeed, JIA treatment is aimed to induce disease remission, and to control pain and preserve range of motion, muscle strength, and function; to manage extra-articular complications; and to enable normal nutrition, growth, and physical and psychological development (2). Pharmacological therapy is based on the combined use of intra-articular (or, less frequently, systemic) glucocorticoids and immunosuppressive medications, like conventional and/or biological disease-modifying antirheumatic drugs (cDMARDs and/or bDMARDs, respectively).

Notably, the earlier introduction of methotrexate (MTX), the more widespread use of intra-articular glucocorticoids, and first and foremost the availability of bDMARDs have led to successful treatment and prevention of long-term sequelae in most patients (4, 5). Along with progresses in therapeutics, a raised expectation for disease control has come, as disease remission (or, at least, a minimal level of disease activity) is an attainable goal in many, if not most, patients (4).

This therapeutic advance has been accompanied by the development and validation of standardized tools for the assessment of JIA disease activity, such as the Juvenile Arthritis Disease Activity Score (JADAS) (6). The JADAS is a composite score of disease activity for JIA, including the following four measures: a count of joint with active disease; physician's global assessment of disease activity, measured on a 0–10 visual analogue scale VAS where 0 = no activity and 10 = maximum activity; parent/patient global assessment of well-being, measured on a 0-10 VAS where 0 = very well and 10 = very poor; and the erythrocyte sedimentation rate (ESR), normalized to a 0 to 10 scale. Based on difference in the joint count, three version of the score have been developed: 1) the JADAS71, including a 71-joint count; 2) the JADAS27, including a 27-joint reduced count; 3) the JADAS10, which is based on the count of any involved joint up to a maximum of ten joints (6). A version of the JADAS yielded by substituting the ESR with the C-reactive protein has also been developed and validated (CRP-JADAS) (7), as well as a three-variable version without the acute phase reactants (clinical JADAS, cJADAS) (8, 9). The cut-offs of the different versions of the JADAS that correspond to the states of inactive disease, minimal, moderate and high active disease have been established (9-11).

That the disease activity of JIA should be assessed and documented regularly using a validated composite instrument is one of the overarching principles included in the recommendations to treat JIA to target (4). The "treat-to-target" strategy in rheumatic diseases consists in the paradigm of explicitly defining a treatment target and applying tight control and necessary therapeutic adjustments to reach the target (4).

According to treat-to-target recommendations for JIA, clinic visits including disease activity assessment should be scheduled every 1-3 months when treating subjects with active disease (4). However, this frequency of visits may not always be possible due

to specific barriers such as geographical and health-system-related constraints and, even in the case of high-quality care, disease activity fluctuations between clinic evaluations may be underrecognized.

In recent years, there has been a growing interest in the use of parent- and child-reported outcomes (PCROs) in JIA (12-14). These measures provide a direct insight on the parent's and child's perceptions of disease course and effectiveness of therapeutic interventions. The incorporation of PCROs in routine assessment of children with JIA may lead to more efficient and effective clinical care, by enforcing concordance with physician's choices, improving treatment adherence, and promoting a shared decision-making strategy (15-18). The identification of valid and reliable PCROs could be crucial to remotely monitor disease activity when in-face evaluation in not possible, as happened during Coronavirus Disease 2019 (COVID-19) pandemic (19).

Several measures for the assessment of PCROs in patients with JIA are currently available, ranging from visual analogue scale (VAS) for rating of child's overall well-being and pain intensity, to questionnaires for the evaluation of functional ability and health related quality of life (HRQOL) (20-25).

The main measures used for the assessment of PCROs in children with JIA have been incorporated in a multidimensional questionnaire, named Juvenile Arthritis Multidimensional Assessment Report (JAMAR), recently translated and cross-culturally validated in the national language of 49 countries (26). Although the JAMAR may be well suited to collect parent- and child-reported information in standard clinical care, it is not specifically aimed to quantify the level of disease activity according to the parent or the child. On the other hand, the identification of a valid tool based on PCROs for the assessment of disease activity is of utmost importance for the development of reliable telemedicine services, which could allow regular remote monitoring of disease course

and therefore lead to the prompt identification of JIA flares, early intervention for patients requiring treatment adjustment, and deferred appointment frequency in case of stable disease.

Given these premises, the main aims of the present Ph.D. thesis were:

1. To report the experience with telemedicine for the management for JIA during COVID-19 pandemic in a tertiary care pediatric rheumatology centre;
2. To select valid and reliable PCROs for the assessment of disease activity in JIA;
3. To develop a new disease activity score for JIA, modeled on the JADAS archetype but solely based on PCROs.

To reach these objectives, the thesis reports the results of different works, listed as follows:

1. A retrospective single centre study describing the impact of COVID-19 related lockdown in a cohort of patients with JIA (chapter 2);
2. Analysis of determinants of parent/patient global assessment of well-being in JIA patients with inactive disease according to the caring physician (chapter 3);
3. Assessment of validity and reliability of 4 PCROs in a multinational sample of children with JIA (chapter 4);
4. Development and initial validation of the parent/child version of the JADAS (chapter 5).

Chapter 2

The role of telemedicine in the management of pediatric rheumatic diseases: lessons from COVID-19 pandemic

Since the beginning of Coronavirus Disease 2019 (COVID-19) outbreak, restrictive measures were implemented to prevent the spreading of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), including the discontinuation of deferrable medical and surgical activities. In this scenario, patients with chronic rheumatic diseases had to cope with important challenges, such as the interruption of non-essential healthcare visits and the concerns raised by the use of immunosuppressive medications, like conventional disease-modifying antirheumatic drugs (cDMARDs) and biologic disease-modifying drugs (bDMARDs) (27). These factors led to dramatic changes in the daily life of patients and in the routine disease management, with a potential negative impact on the disease control, as shown by Roux et al who observed a higher rate of flare in patients with spondylarthritis during the home confinement (28). To assess the lockdown effect on the disease course of our patients with juvenile idiopathic arthritis (JIA), we conducted a single-center retrospective study by comparing the rate of relapse during the lockdown with that observed before COVID-19 pandemic (29). We presented the largest pediatric JIA cohort in which the effects of COVID-19 lockdown on disease course were investigated. Our data showed that more JIA patients experienced a disease flare during the SARS-CoV-2 related home confinement compared to the same period of the previous year (16.9% vs 6.1%), supporting our hypothesis that containment measures during COVID-19 pandemic negatively impacted disease activity. Our findings had a remarkable clinical implication underlying the need for reconsidering home and

healthcare management of children with chronic arthritis during lockdowns aimed to contain pandemics.

It could be argued that the deferral of non-essential healthcare in person consultations during the "phase 1" of COVID-19 pandemic might have led to delays in patients' management thus leading to a worse disease control in our patients. Indeed, the 25% of children included in our study had their visit postponed during the lockdown, however the proportion of delayed face-to-face visits was the same in patients with or without arthritis relapse, suggesting that the limitations in the outpatient visits were not a major contributor to the JIA worsening in our cohort.

That could be explained by the telemedicine service which we provided during the early phases of pandemic. Remote consultations (telephone or email interviews) were performed with patients' parents, investigating the occurrence of signs and symptoms consistent with JIA flare (morning stiffness, joint swelling and/or pain and/or limited range of motion). If any of those was present, in person consultation was ordered. Otherwise, the direct visit was deferred. A considerable proportion of JIA patients were evaluated only through a remote consultation (25%). The remote management of our patients could have limited the impact of deferral of ambulatory services on disease control in our cohort.

Unquestionably, telemedicine had proven itself as a valuable tool during the pandemic, as shown by several studies describing the usefulness of telecounselling to guarantee an effective follow-up of patients with rheumatic diseases despite the restrictive measures (19, 30, 31). Beyond the pandemic, a flexible strategy including both traditional in person consultations and the use of disease activity remote monitoring could lead to a global improvement of the management of rheumatic disorders and a more strict disease control, also reducing the costs of healthcare services (32).

With regard to JIA, the essential contribute of telehealth in its management during SARS-CoV-2 pandemic has also been reported (33, 34). As shown in our study, the use of remote consultation was of utmost importance to limit the negative effect that containment measures could have had on the disease course of our patients. However, subtle signs of active arthritis might have been underrecognized by parents and not reported at telemedicine.

The development of valid and reliable instruments to remotely monitor the disease activity of JIA could limit the potential limitation of the underestimation of active signs of arthritis by the parents and thus increase the reliability of telehealth services in the management of JIA.

The results of our study about the effect of lockdown during COVID-19 pandemic on disease course of JIA have been published in *Arthritis Care & Research (29)*.

Arthritis Care & Research
Vol. 0, No. 0, Month 2022, pp 1–6
DOI 10.1002/acr.24768
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BRIEF REPORT

Increased Relapse Rate During COVID-19 Lockdown in an Italian Cohort of Children With Juvenile Idiopathic Arthritis

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Objective. Changes of routine disease management associated with COVID-19 lockdown might have potentially affected the clinical course of juvenile idiopathic arthritis (JIA). The aim of our study was to assess the rate of disease flare before and during COVID-19 lockdown to investigate its impact on disease course in children with JIA.

Methods. A single-center retrospective study was conducted, including patients presenting with inactive JIA between September 1, 2018 and March 9, 2019 (group A) and between September 1, 2019 and March 9, 2020 (group B). For each patient, demographic and clinical data were collected. The rate of JIA flare from March 10, 2019 to June 30, 2019 for group A and from March 10, 2020 to June 30, 2020 for group B was compared.

Results. Group A included 126 patients, and group B 124 patients. Statistical analysis did not show significant differences among the 2 cohorts with respect to age, sex, age at JIA onset, JIA subtype, co-occurrence of uveitis, antinuclear antibody positivity, and past or ongoing medications. The rate of disease flare during lockdown at the time of the first COVID-19 pandemic wave was significantly higher in comparison to the previous year (16.9% versus 6.3%; P = 0.009).

Conclusion. Our study showed that COVID-19 lockdown was associated with a higher rate of joint inflammation in children with JIA. This finding has a considerable clinical implication, as restrictive measures may be necessary in order to contain pandemics. Our data highlight the need for rearrangement in the home and health care management of children with JIA during lockdowns.

INTRODUCTION

The first European country affected by the COVID-19 pandemic was Italy, where the outbreak exploded in February 2020 having immediately far-reaching health and social implications. Since the beginning of the COVID-19 outbreak, restrictive measures were implemented to prevent the spreading of SARS–CoV-2. During the so-called "phase 1" of the COVID-19 outbreak in Italy, starting on March 10, 2020, school closure was a major component of social distancing along with the shutdown of all nonessential activities, including leisure and sport. During "phase 2," from May 4 to June 15, 2020, there was a progressive easing of the containment measures, although schools and gyms remained closed. While national and regional governments ordered the discontinuation of deferrable medical and surgical activities during phase 1, they were allowed in phase 2.

Children affected by juvenile idiopathic arthritis (JIA) might be considered a vulnerable population. In the first months of the COVID-19 pandemic, JIA patients and their parents had to cope with major challenges in routine disease management, such as limiting nonessential health care visits and physical activity due to home confinement and the concerns raised by the use of immunosuppressive medications, like conventional disease-modifying antirheumatic drugs (cDMARDs) and biologic DMARDs (bDMARDs) (1). These factors might potentially contribute to disease worsening during the pandemic. Current findings on the course of inflammatory rheumatic diseases during lockdown mainly regard adult patients (2–4), while physical effects of the pandemic on pediatric chronic arthritis (5) have not been widely reported. Therefore, we investigated the rate of JIA flare before and during COVID-19 lockdown in order to explore its impact on disease course in children with JIA.

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Author disclosures are available at https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Facr.24768&file=acr24768-sup-0001-Disclosureform.pdf.

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Submitted for publication February 1, 2021; accepted in revised form August 10, 2021.

SIGNIFICANCE & INNOVATIONS

- In this population of children with juvenile idiopathic arthritis from Southern Italy, we observed that COVID-19 lockdown was associated with a higher rate of disease flare.
- Our data underlie the need for reconsidering home and health care management of children with chronic arthritis during lockdowns aimed to contain pandemics.

PATIENTS AND METHODS

A single-center retrospective study was conducted by reviewing medical records of JIA patients admitted at the Pediatric Rheumatology Unit of the University of Naples Federico II with a minimum follow-up duration of 6 months. All patients were diagnosed according to the International League of Associations for Rheumatology criteria (6) and were divided in 2 groups: group A (n = 126; patients with inactive disease between September 1, 2018 and March 9, 2019 [V1] and then reevaluated between March 10, 2019 and June 30, 2019 [V2]); and group B (n = 124; patients with inactive disease between September 1, 2019 and March 9, 2020 [V1] and then reevaluated between March 10, 2020 and June 30, 2020 [V2]).

Inactive disease was defined, according to the American College of Rheumatology (ACR) 2011 criteria (7), as no joint with active arthritis, no systemic manifestations due to JIA, no active uveitis, normal acute-phase reactants, physician global assessment of disease activity (PhGA) indicating no disease activity (defined as score of 0 on a 0–10 visual analog scale), and duration of morning stiffness of <15 minutes. However, the full set of ACR 2011 criteria could not be applied before 2020 due to the limitations in the direct medical visits that precluded a PhGA. In those circumstances, when the other ACR 2011 criteria were met, the absence of disease activity was inferred through the review of the patient chart by consensus of 3 investigators (RN, RA, and MA). Also, patients evaluated with telemedicine tools during COVID-19 lockdown and reporting no signs of active disease were included in group B (n = 31). In fact, during COVID-19 lockdown, remote consultations (telephone or email interviews) were performed with patients' parents, investigating the occurrence of signs and symptoms consistent with JIA flare (morning stiffness, joint swelling and/or pain and/or limited range of motion). If any of those was present, in-person consultation was ordered. Otherwise, the direct visit was deferred. For the purpose of the analysis and in agreement with Beukelman et al (8), patients were grouped in the functional phenotypes of oligoarthritis (≤4 affected joints), polyarthritis (≥5 affected joints), systemic JIA, and enthesitis-related arthritis. Among patients with systemic JIA, only patients with a history of chronic arthritis that persisted in spite of inactive systemic features were included. In order to investigate lockdown effects only on articular symptoms in children with JIA, patients with active uveitis without active arthritis at V2 were excluded from the analysis. A subset of patients included in group A was also evaluated the following year in the same period and thus included also in group B (n = 71).

For each patient, data on demographic characteristics, JIA subtype, age at JIA onset, co-occurrence of uveitis, antinuclear antibody (ANA) positivity, disease duration, and past therapeutic regimens were collected into a dedicated anonymized database. Date of disease onset was defined as the date when the first symptoms of arthritis were noted, as recorded in the clinical charts. For each consultation, data on the PhGA, presence of morning stiffness, presence of JIA flare, including the number and type of active joints (swelling or both tenderness and limited range of motion), erythrocyte sedimentation rate, routine out-of-school physical activity (defined as regular sport activity at least twice a week), and ongoing medications and therapeutic decisions at the visit were also collected. Type of consultation (in-person or remote), missed days of school, and deferred medical visits were also recorded for patients undergoing V2 during the COVID-19 pandemic. Medication adherence was assessed by parental report, including overall adherence (yes/no) and potential barriers. In patients experiencing flares in group B, information on contact history with COVID-19 cases, suspected or confirmed COVID-19 diagnosis before JIA relapse, and the results of SARS–CoV-2 serology, if available, was also investigated and collected.

The JIA relapse rate at V2 was measured and compared between patients of group A and group B. Descriptive statistics were reported as the median and interquartile range (IQR) for continuous variables and as percentages for categorical variables. The rate of disease flare was expressed with 95% confidence intervals (95% CIs). Comparison of categorical variables between the 2 groups was performed by chi-square test or Fisher's exact test in the case of expected frequencies of <5, whereas the Mann-Whitney U test was used in order to compare continuous variables. All statistical tests were 2-sided and considered significant with P values less than 0.05. The study protocol was approved by the Ethical Committee of the University of Naples Federico II (protocol number 440/20).

RESULTS

With regard to group A, 165 patients with JIA presented with inactive disease at V1; of those, 134 underwent V2. Eight subjects with systemic JIA without persistent arthritis were excluded, resulting in a cohort of 126 patients (Figure 1). With regard to group B, 178 patients presented inactive disease at V1, of those 137, underwent V2. One patient with active uveitis at V2 and 12 patients with systemic JIA without history of persistent arthritis were excluded, resulting in a cohort of 124 patients (Figure 1).

Looking at patients' demographic and clinical data (Table 1), in both groups, there was a predominance of female patients

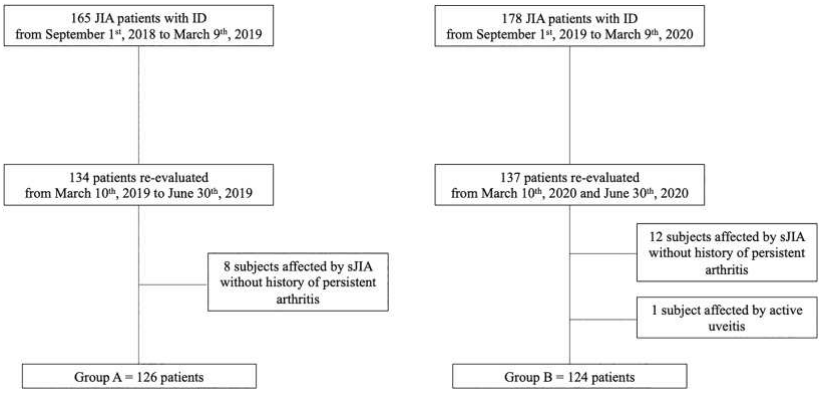

Figure 1. Diagram showing the composition of the patients' groups. Two groups of children with juvenile idiopathic arthritis (JIA) were enrolled, all presenting with clinically inactive disease (ID) at enrollment (V1) and then evaluated (V2) before (group A) and during (group B) the first COVID-19 lockdown. sJIA = systemic JIA.

(77% in group A versus 75.8% in group B; $P = 0.826$), and oligoarticular was the most frequent functional JIA phenotype (65.8% versus 62.1%; $P = 0.534$). No significant difference was observed in regard to age at JIA onset, ANA positivity, and history of uveitis (Table 1). Median age at V1 was 10.9 years in both cohorts; median disease duration at V1 was 5.1 and 5.3 years in group A and B, respectively ($P = 0.809$). No difference was found in the ongoing JIA treatment at V1 (Table 1). Twenty of 126 patients (15.9%) presented with clinical inactive disease without medication in group A compared to 22.6% (28 of 124) subjects in group B ($P = 0.178$). The proportion of patients undergoing treatment with methotrexate was similar (46.8% in group A versus 37.1% in group B; $P = 0.119$), as well as the proportion of subjects treated with a bDMARD (43.7% versus 45.2%; $P = 0.81$). Among patients receiving medication, therapy was tapered or discontinued in 37.7% of patients in group A and 33.3% in group B at V1 ($P = 0.514$). The proportion of children participating in out-of-school physical activities at V1 was ~54% in both cohorts (Table 1). Altogether, these data suggest that clinical and demographic features at baseline did not differ between the 2 groups of patients.

Due to discontinuation of deferrable medical activities, 31 of 124 (25%) patients in group B were evaluated only through a remote consultation at V2; 31 (25%) had their appointment postponed for over a month. At V2, no significant difference was found with respect to the ongoing JIA treatment between the 2 cohorts (Table 2). Temporary drug interruptions for >1 week were reported in 5 of 81 (6.2%) in group B, 4 of which were unrelated to COVID-19. One patient delayed her monthly tocilizumab infusions without medical advice due to fear of being infected but did not develop a flare. The parents of another 10 children expressed worries about continuing drugs for JIA during the pandemic but did not report drug discontinuation. Data on physical activity were available for 77 patients in group A: 48 (62.3%) practiced regular sports activity at V2 in comparison to 4 of 110 (3.6%) in group 2 ($P < 0.00001$). Indeed, 53 of 57 patients (93%) practicing out-of-school physical activity prior to the lockdown had interrupted it for at least 1 month at V2 due to restrictive measures. In addition, patients of group B had not been attending school for a median time of 89.5 days (IQR 71.0–106.7).

The rate of relapse was statistically significantly higher in group B (21 of 124, 16.9% [95% CI 10.8–24.7%]) in comparison to group A (8 of 126, 6.3% [95% CI 2.8–12.1%]) ($P = 0.009$) (Table 2). In fact, a new drug was started in 15.3% of patients of group B compared to 6.3% of group A ($P = 0.022$), while the proportion of patients who underwent therapy tapering or discontinuation at V2 was only slightly lower in group B (15 of 81, 18.5% versus 25 of 90, 27.8%; $P = 0.153$). In more detail, with regard to patients experiencing flares in group B, 16 patients started an NSAID, 4 a new cDMARD or bDMARD, while 3 underwent glucocorticoid joint injection(s), and 3 of 10 required an increased dosage of the ongoing DMARD therapy (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24768).

When considering medication adherence, 11 of 21 relapsing patients in group B were receiving medication at V2. None of these patients reported temporary therapeutic interruptions compared to 5 of 70 children with inactive disease (0% versus 7.1%; $P > 0.05$). The face-to-face visit had been postponed for >1 month in 33.3% of patients who had relapsed (7 of 21), which is the same as for patients presenting with inactive disease (24 of 72, 33.3%; $P = 1$). Data on out-of-school physical activity were available in 18 patients with JIA flare in group 2: 12 of them had interrupted physical activity due to COVID-19 lockdown, and 6 did not practice sports before the COVID-19 pandemic. Of note, none of the patients experiencing flares had either a

Table 1. Baseline characteristics of study patients*

Characteristic	Group A (n = 126)	Group B (n = 124)	P†
Sex, female	97 (77)	94 (75.8)	0.826
Age at JIA onset, median (IQR) years	4 (2.2–6.8)	4.2 (2.0–6.9)	0.71‡
Age at V1, median (IQR) years§	10.9 (7.8–14.4)	10.9 (8.0–14.4)	0.933‡
Disease duration at V1, median (IQR) years§	5.1 (3.2–8.6)	5.3 (2.7–8.5)	0.809‡
JIA subtype			
Oligoarticular	83 (65.8)	77 (62.1)	0.534
Polyarticular	35 (27.8)	41 (33.1)	0.364
Systemic	7 (5.6)	4 (3.2)	0.369
ERA	1 (0.8)	2 (1.6)	0.62¶
ANA positivity	58 (46)	52 (41.9)	0.514
History of uveitis	28 (22.2)	26 (21)	0.81
Past JIA treatment			
Intraarticular glucocorticoid injections	45 (35.7)	40 (32.3)	0.564
Systemic glucocorticoids	21 (16.7)	18 (14.5)	0.639
Methotrexate	54 (42.9)	65 (52.4)	0.13
Other conventional DMARDs	3 (2.4)	2 (1.6)	1.0¶
Biologic DMARDs	14 (11.1)	16 (12.9)	0.663
Ongoing JIA treatment at V1§			
NSAIDs	17 (13.5)	8 (6.5)	0.064
Systemic glucocorticoids	0	1 (0.8)	0.496¶
Methotrexate	59 (46.8)	46 (37.1)	0.119
Sulfasalazine	1 (0.8)	2 (1.6)	0.62¶
Biologic DMARDs	55 (43.7)	56 (45.2)	0.81
Etanercept	28 (22.2)	27 (21.8)	0.932
Adalimumab	15 (11.9)	14 (11.3)	0.879
Infliximab	2 (1.6)	3 (2.4)	0.682¶
Tocilizumab	7 (5.6)	9 (7.3)	0.582
Canakinumab	0	1 (0.8)	0.496¶
Abatacept	3 (2.4)	2 (1.6)	1.0¶
Off-therapy	20 (15.9)	28 (22.6)	0.178
Out-of-school physical activity in the last month, no./total no. (%)#	50/91 (54.9)	50/92 (54.3)	0.9

* Values are the number (%) unless indicated otherwise. ANA = antinuclear antibody; DMARDs = disease-modifying antirheumatic drugs; ERA = enthesitis-related arthritis; IQR = interquartile range; JIA = juvenile idiopathic arthritis; NSAIDs = nonsteroidal antiinflammatory drugs.
† By chi-square test unless otherwise specified.
‡ By Mann-Whitney U test.
§ V1 frame was from September 1, 2018 to March 9, 2019 in group A; and from September 1, 2019 to March 9, 2020 in group B.
¶ By Fisher's exact test.
# Data on sports activity outside school were available for 91 patients in group 1 and for 92 patients in group 2.

suspected or confirmed COVID-19 diagnosis or a COVID-19 exposure, and 5 of them had a negative SARS–CoV-2 serology finding in June 2020.

When comparing patients who had relapsed among the 2 groups, no differences in demographic and clinical features at V2 were found (see Supplementary Table 1, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24768). Notably, ankle arthritis was slightly more frequent in group B (38% versus 0%; $P = 0.066$).

DISCUSSION

To our knowledge, this study presented the largest pediatric JIA cohort in which the effects of COVID-19 lockdown on disease course were investigated. Our data showed that more JIA patients experienced a disease flare during home confinement due to the SARS–CoV-2 pandemic compared to the same period of the previous year, supporting our hypothesis that containment measures during COVID-19 lockdown negatively impacted disease activity.

In contrast to the data published so far about the impact of the COVID-19 pandemic on the course of inflammatory rheumatic diseases in adults (2–4), mostly based on patient-reported data, in our study, disease flare assessment required physician evaluation, thus increasing the strength of our findings. While Ciurea and colleagues found no detrimental impact of containment measures on disease course in 666 patients with spondyloarthritis (SpA), rheumatoid arthritis, or psoriatic arthritis (3), Roux et al observed a significant difference in the rate of severe disease flare in 512 SpA patients before and during home confinement (20% versus 49%) (2). So far, only 1 study reported an increase of JIA flares in a small cohort of 58 children during March to July 2020 (5), in agreement with our findings. The higher relapse rate reported by these 2 latter studies was mainly attributed to

Table 2. Relapse rate and therapeutic regimens in group A and group B at V2*

	Group A (n = 126)	Group B (n = 124)	*P*†
Patients with JIA relapse at V2	8 (6.3)	21 (16.9)	0.009‡
Ongoing JIA treatment at V2			
NSAIDs	6 (4.8)	1 (0.8)	0.120§
Oral glucocorticoids	0	0	
Methotrexate	45 (35.7)	35 (28.2)	0.204
Sulfasalazine	1 (0.8)	2 (1.6)	0.62§
Biologic DMARDs	53 (42.1)	51 (41.1)	0.881
Etanercept	28 (22.2)	26 (21)	0.810
Adalimumab	14 (11.1)	10 (8.1)	0.414
Infliximab	1 (0.8)	3 (2.4)	0.368§
Tocilizumab	7 (5.6)	9 (7.3)	0.582
Canakinumab	0	1 (0.8)	0.496§
Abatacept	3 (2.4)	2 (1.6)	1.0§
Off therapy	36 (28.6)	43 (34.7)	0.299
Therapeutic decision at V2			
Prescription of a new drug	8 (6.3)	19 (15.3)	0.022‡
Continuation of ongoing therapy, no./total no. (%)	57/90 (63.3)	50/81 (61.7)	0.829
Drug dosage increase, no./total no. (%)	3/90 (3.3)	4/81 (4.9)	0.709§
Drug tapering or 1 drug discontinuation, no./total no. (%)¶	25/90 (27.8)	15/81 (18.5)	0.153
Therapy withdrawal, no./total no. (%)	3/90 (3.3)	4/81 (4.9)	0.709§
Out-of-school physical activity in the last month, no./total no. (%)#	48/77 (62.3)	4/110 (3.6)	<0.00001‡

* Values are the number (%) unless indicated otherwise. V2 frame was from March 10, 2019 to June 30, 2019 in group A; and from March 10, 2020 to June 30, 2020 in group B. DMARDs = disease-modifying antirheumatic drugs; JIA = juvenile idiopathic arthritis; NSAIDs = nonsteroidal antiinflammatory drugs.
† By chi-square test unless otherwise specified.
‡ Significant.
§ By Fisher's exact test.
¶ In case of combined medications regimens.
# Data on sports activity outside school were available for 77 patients in group 1 and for 110 patients in group 2.

changes of treatment regimens due to concerns about COVID-19 (2,5). Recently, a large survey did not reveal a decrease in therapy compliance during the first months of the pandemic in ~4,000 patients with rheumatic diseases (9). Accordingly, in our cohort, only 1 patient delayed the scheduled treatment due to apprehension of SARS–CoV-2 infection, down-sizing the possible impact of the pandemic outbreak on treatment adherence and thus on disease course. During lockdown, we remotely recommended patients to continue all therapies as usual, as suggested by the Paediatric Rheumatology European Association in March 2020 (10). This reassurance campaign might have limited the impact of COVID-19–related fears on therapeutic compliance. Yet, a role of decreased drug adherence on disease activity during lockdown could not be entirely excluded, as it was not measured through a validated tool.

During COVID-19 lockdown, children spent less time engaged in physical activity, with a parallel increase in sleeping and TV or video watching/playing time (11,12). These lifestyle modifications may impact on daily life of patients with chronic diseases (13) and possibly contribute to a higher flare rate in children with JIA. As expected, in our population, the proportion of patients performing regular physical activity was significantly lower during the COVID-19 pandemic compared to the previous year. In addition, the children with JIA in our study had not been attending school for ~3 months at the time of consultation. It is well-known that arthritis symptoms worsen in the morning or after prolonged rest (14) and that physical therapy may lead to pain reduction and increased range of motion in JIA patients (15). Indeed, along with medications, exercise is recommended as a therapeutic tool to children and adolescents with JIA in order to counteract the disease-related inflammation and improve clinical symptoms (16). Besides, it has been shown that peripheral blood lymphocytes of less active children present a proinflammatory profile, suggesting that physical activity may decrease systemic inflammatory responses (17). Therefore, the physical inactivity associated with home confinement could be a possible explanation for clinical worsening in our patients. On this basis, we believe that prescription of home-based exercise programs conducted by a physical therapist should be promoted to implement JIA management in case of public lockdowns.

The temporary interruption of nonessential health care in-person consultations during the "phase 1" of the COVID-19 pandemic might have led to delays in patients' management; however, the proportion of delayed face-to-face visits was the same in patients with or without arthritis relapse, suggesting that limitations in outpatient rheumatology medical service were not a main contributor to the worsening of JIA in our cohort. As a matter of fact, outpatient in-person visits were postponed only if parents reported no signs or symptoms consistent with JIA relapse at the telemedicine call. Even though recent data suggest that

telemedicine alone may be insufficient to guide a treat-to-target strategy (18), the use of telehealth tools might have limited the impact of the partial closure of ambulatory services on disease management according to other reports (19). From this point of view, the development of validated telemedicine models for JIA may be critical to guarantee effective management of JIA in case of confinement measures and to monitor disease activity at home.

Our findings should be interpreted within the limitations of the study, which are mainly inherent to its observational and retrospective nature. Besides, our results reflect a single tertiary care center experience, so they may not be extended to other clinical settings. Since our study was not randomized and observational, we cannot exclude that patients in group B presented a more aggressive disease than those in group A. Likewise, the slightly higher number of patients off-therapy in group B may represent a possible confounding factor in our analysis. Nevertheless, the comparison of the 2 cohorts showed homogeneity in regard to demographic and clinical features. Finally, since subtle signs of active arthritis might have been underrecognized and not reported during telemedicine, the relapse rate during lockdown could be even potentially higher than observed.

In conclusion, this study provides new evidence that COVID-19 lockdown was associated with a higher rate of relapse in children with JIA, even in the absence of reduced drug adherence. This finding has considerable clinical implications because restrictive measures are still occurring in several countries as the pandemic evolves. Our data highlight the need for implementing health care management of patients with JIA, including personalized at-home exercise programs in case of new lockdowns.

ACKNOWLEDGMENTS

Open Access Funding provided by Universita degli Studi di Napoli Federico II within the CRUI-CARE Agreement.

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 submitted for publication. Dr. Alessio 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. Naddei, Alessio.
Acquisition of data. Naddei, Alfani, Bove, Mozzillo.
Analysis and interpretation of data. Naddei, Alfani, Discepolo, Guarino, Alessio.

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Chapter 3

What does the parent/patient rating of overall well-being tell us when the physician global assessment score is zero? Analysis of a large multinational dataset

- ***Study conducted, under the mentorship of Professor Consolaro, during Dr. Naddei research fellowship at Istituto Giannini Gaslini, Genoa, Italy***
- ***Manuscript in preparation***

Introduction

Over the past 2 decades, the remarkable advances in the management of juvenile idiopathic arthritis (JIA) have made remission an achievable target for most, if not all, patients (35). The recent treat-to-target recommendations have set the achievement of inactive disease (ID) (or at least a state of minimal active disease) as the primary goal for treatment of patients with JIA (4). ID in JIA can be defined according to two different approaches. The first is based on multiple criteria, all of which should be met, and includes the preliminary criteria for clinical remission (2004 ID criteria) (36) and the American College of Rheumatology provisional criteria for defining clinical ID (2011 ID criteria) (37). The second ID definition is obtained by computing the cutoffs of the juvenile arthritis disease activity score (JADAS) and its three-variable version, the clinical JADAS (cJADAS), that correspond to the state of ID (6, 9-11, 38). Unlike the 2004 and 2011 ID criteria, which are based on physician-reported measures and acute-phase reactants (APR) (36, 37), the JADAS includes a parent/child reported outcome (PCRO) measure, the parent/patient global assessment of well-being (PaGA), in addition to two physician-centered measures (the physician global assessment of overall disease

activity (PhGA) and the count of active joints) and an APR (which is lacking in the cJADAS) (6, 9). Providing a direct insight on the parent's and child's perception of disease course, the incorporation of PCROs in patient assessment may enforce concordance with physician's choices and promote a shared decision-making treatment strategy (15-18). However, the use of the PaGA as an indicator of disease activity in patients with JIA is controversial because it can be affected by several factors in addition to disease activity such as mood, anxiety, pain coping, and family functioning (39). Indeed, discrepancies between the parent/patient's and the physician's components of the scores have been reported (40-42). Some patients may fail to reach remission solely due to poor PaGA rating, despite having no joints with active arthritis, inactive disease according to PhGA and normal acute phase reactants. The failure to attain remission requires therapy adjustment according to the current treat-to-target recommendations (4). Nevertheless, these patients probably do not need pharmacological interventions as the reason for not achieving remission is not the persistence of inflammation. To identify the most suitable intervention in such cases, it appears of utmost importance to understand why some parents/patients rate PaGA poorly despite the absence of inflammatory activity, which might be due to the PaGA measuring a broader construct than PhGA. However, no systematic analysis on the reasons underlying the discordance between PaGA and PhGA in case of inactive joint disease has been published so far.

Against this background, the current study was aimed to identify the determinants of poor PaGA ratings in patients with no active disease according to the caring physician in a large multinational sample of JIA patients.

Methods

Subjects. Data were extracted from a cross-sectional dataset of 9,081 subjects with JIA from 49 countries enrolled in the Epidemiology, treatment and Outcome of Childhood Arthritis (EPOCA) study (43). Briefly, the EPOCA study is a survey conducted by the Paediatric Rheumatology International Trials Organisation (PRINTO) between 2011 and 2016. Each participating centre was asked to enroll all the patients (up to 100) with JIA that were seen consecutively within 6 months. The demographic and clinical features of these patients have been reported elsewhere (43). For each visit, retrospective and cross-sectional data were collected, also including physician-centered measures and the PCROs measures included in the Juvenile Arthritis Multidimensional Assessment Report (JAMAR), a multidimensional questionnaire translated and cross-culturally validated in the national language of 49 countries (26). All participating centers to EPOCA study obtained approval from their respective ethics committee and consent/assent from parents/patients based on existing national regulations.

For the present analysis, we selected patients with a PhGA indicating no disease activity. In the EPOCA study, PhGA was rated on a 21-numbered circle visual analogue scale (VAS), ranging from 0 (no activity) to 10 (maximum activity). Therefore, data from 3,537 patients with a PhGA = 0 were retained.

PaGA and other PCROs collection. In the EPOCA study, at each visit, the JAMAR was proposed for completion to a caregiver and to the patient when he/she was deemed by the caring physician able to understand and respond to the questions in the questionnaire. Data on the following PCROs included in the JAMAR were extracted for the present analysis: 1) PaGA, rated on a 21-numbered circle VAS responding to the following question: “Considering all the ways the illness affects your child, please

evaluate how he/she feels at the moment" (0 = very well, 10 = very poorly) (20). The question was adapted for the patient's self-assessment. 2) The proxy/self-assessment of active joint count, obtained by asking the parent or the child to rate the presence of pain or swelling in the following joints or joint groups: cervical spine, lumbo-sacral spine, shoulders, elbows, wrists, small hand joints, hips, knees, ankles, and small foot joints. Each affected joint/joint group is counted as 1, but the active joint count is cut to a maximum of 10 joints. 3) Pain intensity, rated on a 21-numbered circle VAS (0 = no pain, 10 = extreme pain). 4) Disease activity, rated on a 21-numbered circle VAS (0 = no activity, 10 = maximum activity). 5) Morning stiffness (MS) duration, scored on a 10-point scale as follows: less than 15 minutes (score = 2); 15-30 minutes (score 4); 30 minutes-1 hour (score = 6); 1-2 hours (score = 8); > 2 hours (score =10). The assessment of MS duration was preceded by a question asking whether morning stiffness was present or absent (score = 0). 6) Health related quality of life (HQRoL), assessed through the Pediatric Rheumatology Quality of Life Scale (PRQoL). PRQoL is a 10-item questionnaire that includes 2 subdimensions, physical health (PhH) and psychosocial health (PsH), each composed of 5 items and ranging from 0-15. The total score ranges from 0 to 30, with higher scores indicating worse HRQoL (25). 7) Functional status, assessed through the Juvenile Arthritis Functionality Scale (JAFS) (24). In this 15-item questionnaire, the ability of the child to perform each task is scored as follows: 0 = without difficulty, 1 = with difficulty, 2 = unable to do. The total score ranges from 0 to 30. 8) Listing of medications the child is taking. 9) Description of side effects (SE) of medications.

Statistical analysis. Demographic features, the International League of Associations of Rheumatology (ILAR) category of JIA, the family socio-economic

status, the parent/patient level of education, and the above reported PCROs were compared between subjects with a PaGA $\leq$1 and >1.

Descriptive statistics were reported as median and interquartile range (IQR) for continuous variables and as frequencies (%) for categorical ones. Comparisons of categorical variables were performed by Pearson's $\chi 2$ test or Fisher test if expected frequencies were less than 5. Mann–Whitney U test was used to compare continuous variables between the 2 groups.

To identify variables independently associated with poor PaGA ratings in our sample of JIA patients with ID, a multiple logistic regression analysis was performed, entering explanatory variables that showed significant results in univariate tests ($p< 0.05$) with PaGA > 1 as the outcome variable. Cases with missing variables were excluded from the analysis. Before the application of logistic regression procedures, some continuous variables were dichotomized to binary variables. For age at disease presentation, the cut points chosen were <6 years and >6 years, whereas for age at visit the cut points chosen were <7 years and >7 years. The other numeric explanatory variables were dichotomized as normal or equal to 0 versus altered or greater than 0. Factors retained in the final models were selected by a backward procedure, based on likelihood ratio testing ($p<0.05$). The explanatory power of the model was evaluated by McFadden Pseudo-R^2 (with values between 0.2 and 0.4 indicating excellent model fit) (44) and Tiur's R^2 (45), and by computing the area under the receiver operating curve (AUC-ROC) of the model.

To further explore the relative importance of variables, we employed dominance analysis to rank predictors in terms of their contribution to the overall variance of the outcome, while accounting for their correlations (46). The McFadden R^2 statistic was used to calculate general dominance weights.

All statistical tests were 2-sided; a p-value < 0.05 was considered statistically significant. Rstudio Team (2020, version: 1.3.1093) was used to conduct the statistical analysis. For dominance analysis, the package dominance analysis (V.2.0.0; Claudio Bustos Navarrete and Filipa Coutinho Soares, 2020) was used.

Results

Comparison of clinical features and PCROs between patients with PaGA ≤1 and PaGA>1

675 patients out of the 3,537 (19.1%) included in the analysis had a PaGA >1. Table 1 shows the comparison of demographic and clinical features between patients with PaGA ≤1 and PaGA>1. Compared with patients with PaGA ≤1, patients with PaGA>1 were older at disease onset and at the time of the visit, were more frequently under treatment and had less frequently rheumatoid factor (RF)-positive polyarthritis. No significant differences in gender, family socioeconomic status and parent educational level were found.

The 2 patient groups were significantly different for all PCROs (table 2). Compared to their PaGA≤1 counterparts, subjects with PaGA >1 presented higher parent/patient swollen and/or painful joint count, higher pain and disease activity VAS, higher JAFS and PRQoL scores, and reported more frequently morning stiffness and medications' side effects.

Multivariable analysis of predictors of PaGA>1

For the multivariable analysis, complete data were available on 3,391 patients. The best-fitting model obtained through logistic regression procedures, in which PaGA > 1 was the dependent variable, is presented in figure 1. Independent associations with a PaGA >

1 were identified for age at visit >7, parent/patient swollen and/tender joint count >0, pain VAS > 0, disease activity VAS >0, presence of morning stiffness, impaired functional status and quality of life, and an ILAR category of systemic arthritis. A negative association was found between a PaGA >1 and an ILAR category of RF-positive polyarthritis. The model showed a substantial explanatory power (McFadden R^2=0.33, Tjur's R^2=0.34). The AUC-ROC of the model was 0.8735 (95% confidence interval: 0.859-0.8879).

Dominance analysis

A dominance analysis was conducted to rank the relative contribution of predictive factors in explaining the variance of the outcome (PaGA>1). This analysis showed that the pain VAS > 0, the disease activity VAS > 0 and the PRQoL > 0 were the main determinants of the PaGA>1, accounting for the 19.9%, the 18.6% and the 18.3% of the predicted variance (figure 2).

Discussion

Our results show that in a sizeable proportion of our patients who were judged as having no active disease by the caring physician, parent/patients marked the VAS for PaGA >1. A multivariable analysis and a subsequent dominance analysis identified three explanatory variables as the main determinants of this phenomenon: the pain VAS, the disease activity VAS and the PRQoL. Other drivers included the parent/patient count of swollen and/or tender joints, the presence of morning stiffness, the patient functional ability, the presence of medications' SE, an ongoing treatment for JIA and an older age. The study patients were enrolled at 130 pediatric rheumatologic centers in 49 countries in all continents, thus our population is likely representative of the whole spectrum of

phenotype and severity of children with JIA seen in pediatric rheumatology centers worldwide.

That the PaGA may be scored poorly even when no inflammatory activity is present is a matter of concerns and has important implication for the use of PaGA in the definition of ID when the active joint count and the VAS for PhGA are 0. The condition where patients fail to reach the state of ID solely due to high scores of PaGA represents a dilemma for the physician. According to the treat-to-target recommendations, when the goal of clinical remission is not achieved, treatment should be adjusted (4). Nonetheless, pharmacological interventions may be inappropriate in those patients, given the absence of inflammatory activity.

Based on our results, increased attention should be paid to pain assessment and management in such cases. It has raised considerable concerns that in some children with JIA pain may persist despite adequate treatment with biological agents and satisfactory disease control (47-49). Of course, it is well-know that pain in JIA may be unrelated to disease activity, as happens in case of mechanical pain secondary to structural joint damage or pain amplifications symptoms, which are frequent in pediatric rheumatic diseases (50). These conditions should be promptly recognized and patients be targeted for alternative pain management strategies.

The prominent role of PRQoL in influencing the PaGA confirms that PaGA measures a broader construct that disease activity. This finding is in keeping with what reported by Oen et al, who recently provided evidence of the validity of the PaGA as a measure of HRQoL in children with JIA (51). Noteworthy, in the present study, patients with PaGA ≤ 1 and PaGA >1 differed not only in the PhH-PRQoL and in the assessment of functional ability assessed through the JAFS, but also in the PsH-PRQoL, suggesting that also psychosocial domains affected PaGA scores in our cohort.

We have previously shown that the disease activity VAS possess a good criterion validity for the assessment of disease activity in JIA by exhibiting fair correlation with the PhGA and reaching correlations with physician reported measures at greater levels compared to the PaGA (52). However, in the present study, subjects with PaGA >1 rated the disease activity VAS with higher scores, resulting in a discordance between the physician's and the parent/patient's assessment of disease activity in a sizeable proportion of patients.

It is worthy to mention that, although showing a lower impact on PaGA at the dominance analysis, also an ongoing treatment for JIA and the presence of medication SEs resulted predictors of poorer PaGA in patients without active joint disease, suggesting that the treatment burden plays a major role in the parent/patient perception of disease course, as already reported (53). This finding has a considerable implication, showing that not only an optimal control of medication SEs but also a timely de-escalation of treatment could lead to better parent/patient outcomes.

In conclusion, our study confirms that many patients mark the PaGA >1 in absence of inflammatory activity according to the caring physician, showing that to patients not always abrogation of inflammation means remission. The presence of pain and the impairment of physical and psychosocial quality of life appear to be the main determinants of this discordance, suggesting that PaGA reflects many aspects of the disease burden, including not only disease activity, but also non-inflammatory pain, functional ability, treatment burden and psychosocial aspects. Therefore, when no signs of active disease are present, but the parent/patient perception of disease is still poor, it is not the time to reinforce of disease-modifying medications, but rather to seek for the reasons of such discordance, by exploring the above-mentioned domains. Adjuvant tailored interventions, including exercise or physical therapy, psychosocial support,

occupational therapy, should be considered in such cases to alleviate the disease burden in these patients, beyond what is achieved through the abrogation of inflammation.

Tables

Table 1. Comparison of demographic and clinical features between patients with JIA and no disease activity according to the caring physician who had the PaGA scored as ≤1 or >1.

	Patients with PaGA≤1 N=2,862	**Patients with PaGA>1** N=675	**p-value**
Female (%)	1,866 (65.2)	448 (66.4)	0.604
Median (IQR) age at disease onset, years	4.4 [2.1, 8.6]	5.7 [2.7, 9.6]	<0.001
Median (IQR) age at visit, years	11.0 [7.1, 14.3]	12.3 [8.4, 15.6]	<0.001
ILAR category (%)			0.027
Systemic arthritis	343 (12.0)	82 (12.1)	
Oligoarthritis	1399 (48.9)	294 (43.6)	
RF negative polyarthritis	596 (20.8)	149 (22.1)	
RF positive polyarthritis	71 (2.5)	10 (1.5)	
Psoriatic arthritis	88 (3.1)	26 (3.9)	
Enthesitis related arthritis	236 (8.2)	71 (10.5)	
Undifferentiated arthritis	129 (4.5)	43 (6.4)	
Under treatment (%)	1,919 (67.2)	540 (80.2)	<0.001
Family socioeconomic status (%)			0.781
Low	421 (17.6)	92 (18.1)	

Average	1,685 (70.5)	360 (71.0)	
High	285 (11.9)	55 (10.8)	
Parent educational level (%)			0.422
Elementary or lower	420 (20.2)	95 (22.0)	
High school	1,015 (48.9)	216 (50.1)	
Degree	640 (30.8)	120 (27.8)	

PaGA = Parent/patient global assessment of well-being; IQR = interquartile range; ILAR = International League of Associations of Rheumatology; RF = Rheumatoid factor.

Table 2. Comparison of PCROs between patients with JIA and no disease activity according to the caring physician who had the PaGA scored as ≤1 or >1.

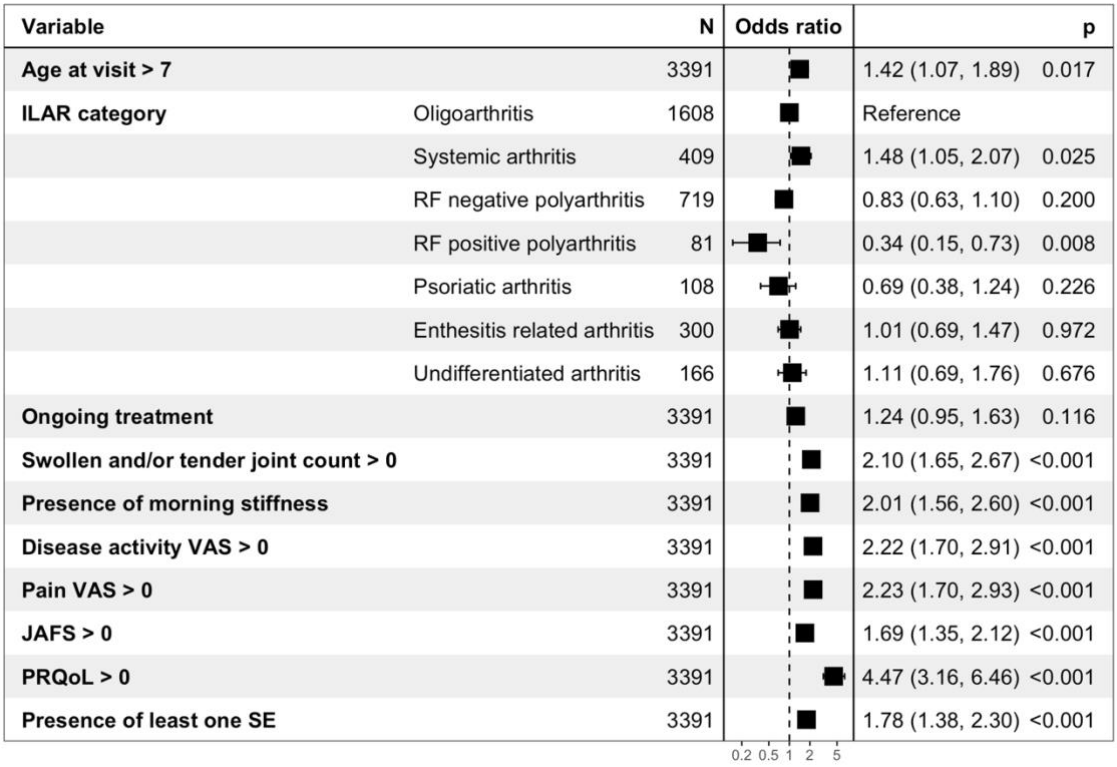
	Patients with PaGA≤1 N=2,862	**Patients with PaGA>1** N=675	**p-value**
Reporting at least one swollen and/or tender joint (%)	365 (12.8)	358 (53.0)	<0.001
Swollen and/or tender joint count (median [IQR])	0.0 [0.0, 0.0]	1.0 [0.0, 2.0]	<0.001
Presence of morning stiffness (%)	227 (8.0)	285 (42.4)	<0.001
Disease activity VAS > 0 (%)	626 (22.2)	498 (74.2)	<0.001
Disease activity VAS (median [IQR])	0.0 [0.0, 0.0]	2.0 [0.0, 3.5]	<0.001
Pain VAS > 0 (%)	590 (20.7)	497 (74.0)	<0.001
Pain VAS (median [IQR])	0.0 [0.0, 0.0]	2.0 [0.0, 4.0]	<0.001
JAFS score > 0 (%)	642 (22.5)	415 (61.8)	<0.001

JAFS score (median [IQR])	0.0 [0.0, 0.0]	1.0 [0.0, 4.0]	<0.001
PRQoL > 0 (%)	1,440 (51.1)	617 (93.9)	<0.001
PRQoL score (median [IQR])	1.0 [0.0, 2.0]	6.0 [3.0, 9.0]	<0.001
PhH PRQoL (median [IQR])	0.0 [0.0, 1.0]	3.0 [1.0, 5.0]	<0.001
PsH PRQoL (median [IQR])	0.0 [0.0, 1.0]	3.0 [1.0, 5.0]	<0.001
Reporting at least one medications' side effect (%)	422 (22.2)	236 (43.9)	<0.001
Medications' side effects (median [IQR])	0.0 [0.0, 0.0]	0.0 [0.0, 1.0]	<0.001

PaGA = Parent/patient global assessment of well-being; IQR = interquartile range; VAS = visual analogue scale; JAFS = Juvenile Arthritis Functionality Scale; PRQoL = Pediatric Rheumatology Quality of Life Scale. PsH = physical health; PsH = psychosocial health.

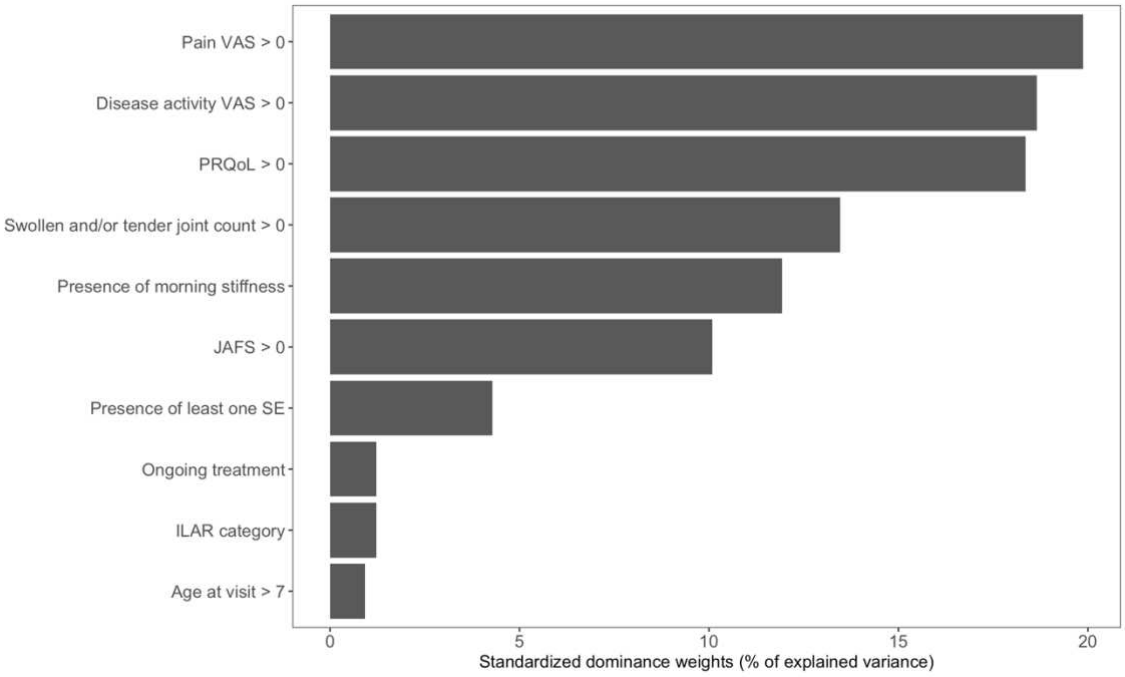
Figures

Figure 1. Forest plot based on the results of multivariable logistic regression analysis of the factors associated with a PaGA>1 in patients with JIA having a PhGA = 0. Complete data were available on 3,391 patients.



ILAR = International League of Associations of Rheumatology; VAS = visual analog scale; JAFS = Juvenile Arthritis Functionality Scale; PRQoL = Pediatric Rheumatology Quality of Life Scale; SE = side effects.

Figure 2. Dominance analysis of relative importance of predictive factors in explaining the variance in parent/patient global assessment of well-being. The average contribution of each covariate is standardized to be out of 100% (ie, divided by the sum of the general dominance weight of all variables, R^2=0.33) and reported as percentage of contribution to the predicted variance.



VAS = visual analogue scale; PRQoL = Pediatric Rheumatology Quality of Life Scale; JAFS = Juvenile Arthritis Functionality Scale; SE = side effect; ILAR = International League of Associations of Rheumatology.

Chapter 4

Implementing the recommendations of the OMERACT: assessment of the validity of parent/patient–reported outcome measures for JIA remote monitoring

- ***Study conducted, under the mentorship of Professor Consolaro, during Dr. Naddei research fellowship at Istituto Giannini Gaslini, Genoa, Italy***

The Outcome Measures in Rheumatology (OMERACT) is an international, independent entity of stakeholders, including health professionals, methodologists, and patient research partners devoted to outcome measures in rheumatology (54). OMERACT strives to improve endpoint outcome measurement through a data driven, iterative alignment process aimed to endorse valid, responsive, feasible health outcome measures/scales in patients with musculoskeletal condition. The initiatives of OMERACT are carried out by participants within various working groups who work on the development of the OMERACT research agendas (55).

OMERACT depicts domains to be used as endpoint in clinical studies as a 3-layered "onion": (a) inner circle: core set of domains mandatory for all randomized clinical trials and longitudinal observational studies, (b) middle circle: important domains with optional inclusion, and (c) outer circle: "research agenda".

The OMERACT juvenile idiopathic arthritis (JIA) Working Group has recently updated the core set of domains to be considered for JIA (56). Unlike the former core set (57), developed without the input of patients/parents, JIA patients, their parents, and parents' associations were involved in the identification and ranking of the most relevant disease domains by OMERACT for the development of the new core set of domains for

JIA (56, 58). Candidate domains were identified through literature review, qualitative surveys, and online discussion boards held with patients with JIA and parents in Australia, Italy, and the United States. A Delphi survey with parents, patients, healthcare providers, researchers, and regulators was implemented to revise the domain list and select the domains. After the presentation of results, OMERACT workshop participants voted, with consensus set at > 70%. Figure 1 shows the new OMERACT Onion framework, based on the results of the Delphi process.

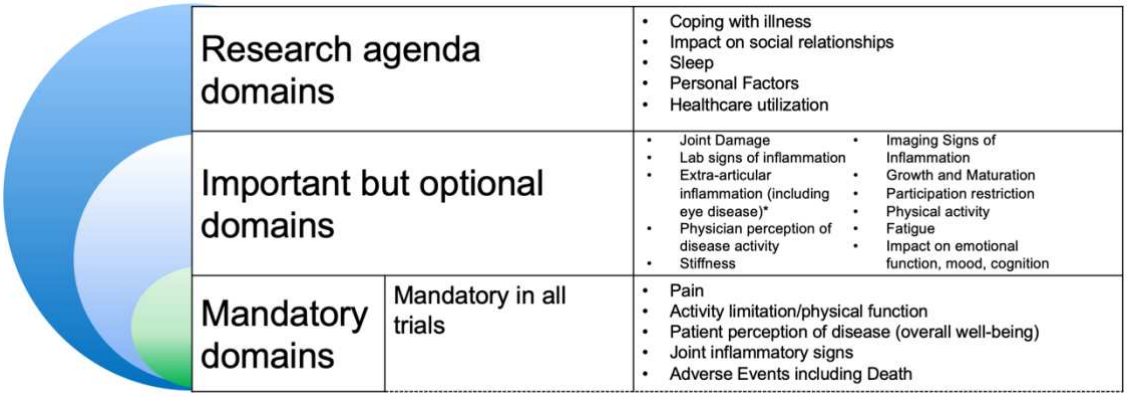


Figure 1. OMERACT domain framework for juvenile idiopathic arthritis (JIA) studies (55, 56).

The updated JIA core domain set has increased emphasis on patient/parent-reported domains, meeting the need of including patient/parent perspective as endpoint in clinical studies on JIA. In fact, the domains not only may refer to physician-reported measures or laboratory exams but also to parent/child reported outcomes measures (PCROs). The new core set includes 5 components which are pain, physical function, patient perception of the disease (overall well-being), joint inflammatory signs and adverse events, 3 of which —pain, physical function, and overall well-being— are based on patient self-ratings. Moreover, joint inflammatory signs could be assessed by both a physician and a parent or patient. The important but optional domains also include

components based on the parent/child perception, such as stiffness, fatigue, and disease impact on emotional function, mood and cognition.

In conclusion, OMERACT has provided an updated core set domain for JIA, shedding the light also on the importance of components related to the parent/patient perspective of disease. As pointed out by the authors, the further steps will be to identify and evaluate the best outcome measures for these domains.

With this purpose, we conducted a study to test the criterion validity and reliability of four PCRO measures for JIA (pain, disease activity, proxy/self-joint count, and morning stiffness), related to disease activity, which referring domains are included in the OMERACT JIA domains framework (52). Particularly, three of the selected measures (pain, disease activity and joint count) refer to domains indicated as mandatory by the OMERACT workshop, whereas stiffness is considered an important, even though optional, domain (56).

To provide adequate strength to the validation process, it was conducted in a large sample comprising more than 6,000 patients from several different countries, included in the Epidemiology, treatment and Outcome of Childhood Arthritis (EPOCA) study (43), thus our results are probably generalizable to patients with juvenile idiopathic arthritis worldwide. All the four tested measures yielded moderate correlations with the physician reported measures, such as the physician global assessment and the number of active joints, and moderate-to-strong correlations with the composite disease activity scores, such as the Juvenile Arthritis Disease Activity Score (JADAS) (6) or its version lacking the acute phase reactant, the clinical JADAS (cJADAS) (9). The level of correlation remained stable irrespective of the socioeconomic status of family and the parent education level, and after grouping patients by geographic area also. These data indicated that the four measures possess a good criterion validity, regardless of patient geographical

origin or family social context. The four PCROs also obtained correlations in a strong range both in inter-rater and in test-retest reliability analysis, showing to be very reliable tools.

In conclusion, taking advantage of the initiative of the OMERACT Working Group, which shed further lights on the necessity of the use of PCROs in the evaluation of JIA, we provided evidence of the validity and reliability of four PCROs for JIA, showing that they are valid and reliable instruments for patient/parent evaluation of disease activity in JIA (52). Those PCROs could be used not only in a research setting but also in the standard clinical care, and are ideally suited to be included in a parent/patient reported disease activity score for remote monitoring of patients.

The results of this study have been published in *Arthritis Care & Research (52)*.

Check for updates

Arthritis Care & Research
Vol. 0, No. 0, Month 2022, pp 1–10
DOI 10.1002/acr.24855
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Validity and Reliability of Four Parent/Patient–Reported Outcome Measures for Juvenile Idiopathic Arthritis Remote Monitoring

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Objective. The aim of this work was to provide evidence of validity and reliability for 4 parent/child–reported outcome measures included in the Outcome Measures in Rheumatology juvenile idiopathic arthritis core domain set: the evaluation of the child's pain and level of disease activity, the assessment of morning stiffness duration, and an active joint count for proxy/self-assessment.

Methods. Patients were included in the multinational study Epidemiology Treatment and Outcome of Childhood Arthritis. Criterion validity was assessed by examining the correlation of the 4 tested measures with physician measures and the clinical Juvenile Arthritis Disease Activity Score in 10 joints (cJADAS10) in the whole sample and after grouping patients by International League of Associations for Rheumatology (ILAR) category, geographic area, and education level. Reliability was assessed comparing 2 visits 7–14 days apart with intraclass correlation coefficients (ICCs).

Results. A total of 8,643 parents and 6,060 patients had all the evaluations available. Correlations of tested measures were moderate (0.4–0.7) with physician-reported measures. The level of correlation with the cJADAS10 remained stable after grouping patients by ILAR category, geographic areas, and level of education of the parent filling the questionnaire. In 442 parents and 344 children, ICCs ranged between 0.79 and 0.87 for parents and 0.81 and 0.88 for children.

Conclusion. The 4 tested parent/child–reported outcomes showed good criterion validity and excellent reliability. These tools can be considered for remote patient assessment, when in-person evaluation might not be possible.

INTRODUCTION

In recent years, the interest in the assessment of parent/child–reported outcomes in pediatric rheumatic diseases has gained increasing importance (1–3). These measures reflect the parent's and child's perception of the disease course and effectiveness of therapeutic interventions. The integration of these perspectives in clinical assessment may facilitate concordance with physicians' choices and improve adherence to treatment and participation in a shared decision-making strategy (4–6). In

Supported by IRCCS Istituto Giannina Gaslini.

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Author disclosures are available at https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Facr.24855&file=acr24855-sup-0001-Disclosureform.pdf.

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Submitted for publication September 30, 2021; accepted in revised form December 30, 2021.

SIGNIFICANCE & INNOVATIONS

- The integration of parent/child–reported outcomes in clinical assessment may facilitate concordance with physicians' choices and improve adherence to treatment and participation in a shared decision-making strategy in juvenile idiopathic arthritis.
- The selected measures of parent/patient assessment of pain, disease activity level, joints with active arthritis, and morning stiffness were valid and reliable tools for patient self-monitoring.
- The selected measures are ideally suited for remote assessment of disease course and could potentially be included in a patient/parent–reported disease activity score for juvenile idiopathic arthritis.

addition, the use of parent/child–reported outcomes may help the physician to identify with greater accuracy the salient issues for each patient and to focus the attention on relevant matters. Thus, information obtained from the parent or the child may contribute to the success of patient care (7). Moreover, the availability of reliable parent/child–reported outcomes could be crucial for remote monitoring of patients when in-person clinical evaluation may be difficult or even impossible.

The Outcome Measures in Rheumatology (OMERACT) Juvenile Idiopathic Arthritis (JIA) Working Group has recently provided a new core set of domains to be considered for the evaluation of children with JIA. JIA patients, their parents, and parents' associations other than clinicians and researchers expert in pediatric rheumatology, contributed substantially to the identification and ranking of the most relevant disease domains (8,9). Consensus methods and selection of domains procedure have been described in detail elsewhere (9). The domains may refer to physician-reported measures, parent/child–reported outcomes, or laboratory examinations; some domains, such as the joint inflammatory signs, could be assessed by both a physician and a parent or patient. The aim of this work was to provide further evidence of validity and reliability for 4 parent/child–reported outcome measures, domains included in the OMERACT JIA core domain set. Among the domains that can be assessed by a parent/patient–reported measure, those that obtained the highest ranking after consensus voting were "pain" and "joint inflammatory signs/active joints."

Pain is the most relevant symptom of children with JIA (10). Several studies have shown that pain is more prevalent in JIA than previously recognized and that a sizeable percentage of patients continue to report pain long after disease onset (11). High levels of pain limit physical activities, disrupt school attendance, and contribute to psychosocial distress. These issues make reduction of pain a key goal of treatment, and therefore the identification of a reliable tool to measure this domain is of major importance.

The evaluation of joint inflammatory signs and the count of joints with active disease is traditionally considered a physician-reported domain. Joint count assessment by physicians through swollen and tender joints is considered the most conventional way of detecting clinical synovitis (12), and its importance in disease activity assessment is supported by the inclusion of joint counts in core data sets of disease activity indices such as the Juvenile Arthritis Disease Activity Score (JADAS) (13) and the American College of Rheumatology (ACR) pediatric response criteria (14) used in clinical trials, research, and clinical practice. Although only few data are available on self- or proxy-reported joint count in JIA (15), a recent systematic literature review in adults with rheumatoid arthritis (RA) showed that patient-reported joint counts have a potential role in the monitoring of disease activity, with satisfactory intraobserver and interobserver reliability (16).

Another domain that was highly ranked in the process leading to the development of the OMERACT JIA core domain set is the "patient's perception of disease/overall well-being." Surprisingly, physicians and other stakeholders considered this domain as more important than parents and patients. The domain of a patient's perception of disease activity is traditionally measured by the patient's global assessment or well-being scale, such as in all the JADAS versions. Overall well-being, or global health, and the patient's perception of disease activity, however, should probably be considered as different domains, with the former being broader and probably including the latter. Conceptually "global health" includes several aspects of health outcomes, that is, also those unrelated or not directly related to disease activity (17). The most widely adopted disease activity indices for RA include a patient self-report measure. In the Simplified Disease Activity Index and the Clinical Disease Activity Index, this item is defined as "patient global assessment of disease activity," whereas it is defined as "global health" in the Disease Activity Score (DAS) and in the 28-joint DAS (18,19). A measure of parent/patient perception of disease activity is available for JIA (20), but so far, that measure has never been incorporated in disease activity scores or in core measurement sets.

Finally, we decided to include in the study a fourth domain, "stiffness," which was also highly ranked in the OMERACT core domain set consensus process. Morning stiffness is a major symptom of active disease in children with JIA and may have a profound impact on physical function and health-related quality of life (21,22). Assessment of morning stiffness was incorporated in the 2011 criteria for clinically inactive disease in JIA; patients can satisfy the definition of clinically inactive disease only if they have morning stiffness lasting ≤15 minutes (23). This cutoff was based on the belief that morning stiffness ≤15 minutes may represent damage from previous active disease or may be due to reasons other than active inflammation. Further analyses have shown that the presence of morning stiffness in JIA patients classified to be in clinically inactive disease by formal definitions is associated with worse parent perception of a child's health and disease status (24). Furthermore, morning stiffness was also a

consistent predictor of worse outcome in various categories of JIA patients (25).

The aim of this study was to provide evidence of validity and reliability for 4 outcome measures assessing the parent/patient–reported domains of pain, joint inflammatory signs, patient's perception of disease, and morning stiffness. The selected tools are included in the Juvenile Arthritis Multidimensional Assessment Report (JAMAR), which was recently translated and cross-culturally validated in the national language of 49 countries (26). These tools can be considered for inclusion in a parent/patient disease activity score.

PATIENTS AND METHODS

Subjects. Patients' data were obtained from a large multinational data set of subjects enrolled in the Epidemiology Treatment and Outcome of Childhood Arthritis (EPOCA) study (27). Briefly, the EPOCA study is a survey conducted by the Pediatric Rheumatology International Trials Organization between 2011 and 2016, involving 9,081 JIA patients from 130 pediatric rheumatology centers in 49 countries, grouped into 8 geographical areas. Each participating center was asked to enroll 100 patients meeting the International League of Associations for Rheumatology (ILAR) criteria for JIA that were seen consecutively over 6 months or, if the center did not expect to see at least 100 patients within 6 months, to enroll all patients seen consecutively within the first 6 months after study start. Patients were included irrespective of their disease duration. For each visit, retrospective and physician-reported data were collected, together with parent/child–reported outcomes included in the JAMAR, filled by a legal guardian and, when appropriate, by the patient. Ethical approval was obtained in all countries involved in the EPOCA study.

Outcome measures. In the EPOCA study, the questionnaire was proposed for completion by a caregiver (proxy-reported measure) and by the patient when he/she was deemed by the caring physician able to understand and respond to the questions in the JAMAR (self-reported measures). In some instances, the questionnaire was filled only by the patient.

The intensity of the child's pain was rated on a 21-numbered circular scale corresponding to the traditional visual analog scale (VAS; 0 = no pain, 10 = extreme pain) (28), responding to the question "How much pain has your child had because of the illness over the past week?" The question was adapted for the patient's self assessment.

The level of the child's disease activity was also rated on a 21-numbered circular scale (0 = no activity, 10 = maximum activity), responding to the question "Considering all the symptoms, such as pain, joint swelling, morning stiffness, fever (if due to arthritis), and skin rash (if due to arthritis), please evaluate the level of activity of your child's illness at the moment." The question was adapted for the patient's self assessment.

The duration of morning stiffness was measured with a 5-point Likert scale, with the following anchors: "less than 15 minutes," "15–30 minutes," 30 minutes to 1 hour," "1–2 hours," and "more than 2 hours." The assessment of morning stiffness duration was preceded by a question asking whether morning stiffness was present or absent.

The proxy- and self-assessment of joint inflammatory signs was obtained by asking the parent or the patient to rate the presence of pain or swelling in the following joints or joint groups, listed in a table: cervical spine, lumbo-sacral spine, shoulders, elbows, wrists, small hand joints, hips, knees, ankles, and small foot joints. Patients or parents had to mark with an "X" by the affected joint/joints group. To each joint or joint group, 1 point was given in case of monolateral involvement and 2 points in case of bilateral involvement, if applicable. The sum obtained yielded the parent/patient joint count, with a score range of 0–18.

Validity. Criterion validity of tested measures was assessed by examining the correlation of the 4 tested measures with physician-reported measures, an acute phase reactant (erythrocyte sedimentation rate [ESR]), and composite disease activity scores. Physician measures included the physician global assessment (PhGA) on a 0–10 scale, the number of joints with active arthritis, swollen joint count, tender joint count, and the number of joints with limitation on motion. Composite scores included the clinical JADAS in 10 joints (cJADAS10). The cJADAS10 is given by the sum of the PhGA, the parent/patient assessment of well-being on a 0–10 VAS, and the number of joints with active arthritis cut at 10. For each analysis, the correlations of the well-being VAS with physician-reported measures and ESR were also presented, as a reference. Correlations of the well-being VAS with the composite scores were not considered, the former being part of the latter.

To further assess the validity of the tools, correlations of the parents' and patients' measure with the cJADAS10 were also computed after grouping patients by ILAR category and by geographic area (northern Europe, western Europe, southern Europe, eastern Europe, North America, Latin America, Africa and Middle East, and southeast Asia). Correlations of parents' measures were also analyzed grouped by family socioeconomic status (subjectively rated by the attending physician as low, average, or high), and by education level (elementary or lower, high school, or degree) of the parent completing the questionnaire. Finally, correlations of patients' measures were analyzed after grouping subjects into 4 age groups: "6–10 years," "11–13 years," "14–18 years," and ">18 years."

Correlations were computed using Spearman's rank correlation method. Correlations were considered high if >0.7, moderate from 0.4–0.7, and low if <0.4 (28). We expected that correlations

of tested tools would be higher with those measures more closely related to disease activity, such as the number of joints with active arthritis or the PhGA. Moreover, we expected that correlations would be higher with the composite score, because it includes a parent/child–reported outcome.

Reliability. When both parent's and patient's evaluations were available at the same visit, the Spearman's correlation (95% confidence interval) between the parent's and the child's rating of the 4 tested measures were calculated to demonstrate the interrater reliability of the tools. To assess test–retest reliability, a randomly selected subset of subjects was asked to complete the JAMAR again 7–14 days after the first time. In this subset of subjects, test–retest reliability of each measure was assessed with the intraclass correlation coefficient (ICC), using a 2-way mixed-effects model. The ICC was classified as follows: <0.2 = poor, 0.2–0.39 = fair, 0.4–0.59 = moderate, 0.6–0.79 = substantial, and ≥0.80 = almost perfect reproducibility (29). Test–retest reliability for individual measures was further examined by the Bland-Altman approach (30) to test for random error of each variable. In this approach, the differences between the first and second measurement were plotted against their means. The mean difference ±1.96 × SD with its resulting interval represents 95% limits of agreement.

RESULTS

Descriptive characteristics of patients. A total of 8,643 parents and 6,060 patients had all the evaluations available for the tested tools in the EPOCA data set. In 5,947 instances, the questionnaire was filled by the patient and a parent at the same visit. Demographic figures, disease activity parameters, and parent/child–reported outcomes of patient samples are shown in Table 1.

Validity correlations. In the EPOCA parents' data set, correlations of all tested measures are in the moderate range with physician-reported measures of disease activity, with the exception of morning stiffness (ρ = 0.17–0.24) and in the poor range with the limited joint count (ρ = 0.30–0.41) and with ESR (ρ = 0.32–0.43). Correlations of the parent/patient joint count, the disease activity scale, and the pain scale were strong with the cJADAS10 (Table 2). Correlations of patient-reported measures were similar.

The level of correlation of the tested parent measures with the cJADAS10 remained stable after grouping patients by ILAR category (Figure 1A). Similar results were obtained for patient measures (see Supplementary Figure 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24855). In the same analysis with patients grouped in 8 geographic areas, correlation levels were similar, although on average, they were higher in Latin America and slightly lower in North America (Figure 1B for parents' measures, and for patients see Supplementary Figure 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24855).

In 6,287 patients in the EPOCA data set for whom these data were available, the level of correlation of the 4 measures with the cJADAS10 did not change according to the level of education of the parent completing the questionnaire (data not shown). Finally, in 7,336 subjects, correlations remained in the same category across 3 different categories of socioeconomic status (low,

Table 1. Descriptive statistics of the EPOCA patient samples*

	Parents (n = 8,643)	Patients (n = 6,060)
Female, no. (%)	5,756 (66.6)	3,968 (65.5)
Age at onset, years	5.4 (2.4–9.6)	7.3 (3.6–10.8)
Age at visit, years	11.3 (7.4–14.6)	13.1 (10.5–15.5)
ILAR category, no. (%)		
Systemic arthritis	928 (10.7)	812 (13.4)
Persistent oligoarthritis	2,750 (31.8)	717 (11.8)
Extended oligoarthritis	931 (10.8)	1,573 (26.0)
RF-negative polyarthritis	2,028 (23.5)	220 (3.6)
RF-positive polyarthritis	355 (4.1)	1,474 (24.3)
Psoriatic arthritis	287 (3.3)	329 (5.4)
Enthesitis-related arthritis	880 (10.2)	626 (10.3)
Undifferentiated arthritis	484 (5.6)	309 (5.1)
Socioeconomic status, no. (%)		
Low	1,401 (19.6)	1,018 (20.6)
Average	4,954 (69.4)	3,399 (68.7)
High	786 (11.0)	533 (10.8)
Education, no. (%)		
Elementary or lower	1,492 (24.4)	1,112 (26.6)
High school	2,823 (46.2)	1,956 (46.7)
Degree	1,790 (29.3)	1,120 (26.7)
Physician global assessment	1.0 (0.0–3.0)	1.0 (0.0–3.0)
Swollen joint count	0.0 (0.0–1.0)	0.0 (0.0–1.0)
Tender joint count	0.0 (0.0–1.0)	0.0 (0.0–2.0)
Joints with motion limitation	0.0 (0.0–2.0)	0.0 (0.0–2.0)
Joints with active arthritis	0.0 (0.0–2.0)	0.0 (0.0–2.0)
Erythrocyte sedimentation rate	10.0 (5.0–20.0)	10.0 (5.0–20.0)
JADAS10	3.5 (0.5–9.0)	3.5 (0.5–9.0)
cJADAS10	3.0 (0.5–8.0)	3.0 (0.5–8.0)
JADAS10 disease state, no. (%)†		
Inactive disease	3,874 (44.8)	2,689 (44.4)
Minimal disease activity	1,442 (16.7)	1,009 (16.7)
Moderate disease activity	2,676 (31.0)	1,900 (31.4)
High disease activity	651 (7.5)	462 (7.6)
Pain VAS	1.0 (0.0–3.5)	1.0 (0.0–3.5)
Parent joint count	1.0 (0.0–2.0)	1.0 (0.0–2.0)
Morning stiffness	0.0 (0.0–1.0)	0.0 (0.0–1.0)
Disease activity VAS	1.0 (0.0–3.5)	0.5 (0.0–3.5)
Well-being VAS	1.0 (0.0–3.5)	0.5 (0.0–3.5)

* Values are the median (interquartile range) unless indicated otherwise. cJADAS10 = clinical Juvenile Arthritis Disease Activity Score in 10 joints; EPOCA = Epidemiology Treatment and Outcome of Childhood Arthritis; ILAR = International League of Associations for Rheumatology; RF = rheumatoid factor; VAS = visual analog scale.
† According to the American College of Rheumatology 2021 JADAS10 cutoffs (ref. 31).

Table 2. Spearman's correlations of the parent- and patient-reported outcomes with physician's and laboratory measures in EPOCA data sets*

	PhGA	NAJ	SJC	TJC	NLJ	ESR	cJADAS10
Parent-reported outcomes							
Parent joint count	0.59 (0.58, 0.61)	0.56 (0.54, 0.57)	0.5 (0.48, 0.52)	0.57 (0.55, 0.58)	0.41 (0.39, 0.43)	0.24 (0.22, 0.26)	0.69 (0.68, 0.71)
Morning stiffness	0.43 (0.41, 0.44)	0.35 (0.33, 0.37)	0.32 (0.3, 0.34)	0.43 (0.42, 0.45)	0.3 (0.28, 0.32)	0.17 (0.14, 0.19)	0.53 (0.51, 0.54)
Disease activity VAS	0.6 (0.58, 0.61)	0.48 (0.47, 0.5)	0.43 (0.41, 0.45)	0.53 (0.51, 0.54)	0.37 (0.35, 0.39)	0.24 (0.21, 0.26)	0.73 (0.72, 0.74)
Pain VAS	0.57 (0.55, 0.58)	0.45 (0.43, 0.46)	0.39 (0.37, 0.41)	0.55 (0.53, 0.56)	0.35 (0.33, 0.37)	0.22 (0.19, 0.24)	0.71 (0.7, 0.73)
Well-being VAS	0.54 (0.53, 0.56)	0.43 (0.41, 0.45)	0.38 (0.36, 0.39)	0.5 (0.48, 0.52)	0.35 (0.33, 0.36)	0.22 (0.2, 0.24)	0.82 (0.82, 0.83)
Patient-reported outcomes							
Patient joint count	0.58 (0.56, 0.59)	0.52 (0.5, 0.54)	0.46 (0.44, 0.48)	0.58 (0.56, 0.6)	0.37 (0.35, 0.39)	0.21 (0.18, 0.24)	0.68 (0.66, 0.69)
Morning stiffness	0.42 (0.4, 0.45)	0.35 (0.33, 0.37)	0.31 (0.29, 0.33)	0.43 (0.41, 0.45)	0.27 (0.25, 0.3)	0.15 (0.13, 0.18)	0.52 (0.5, 0.54)
Disease activity VAS	0.59 (0.57, 0.6)	0.47 (0.45, 0.49)	0.41 (0.39, 0.44)	0.53 (0.51, 0.55)	0.34 (0.32, 0.36)	0.21 (0.19, 0.24)	0.71 (0.7, 0.72)
Pain VAS	0.56 (0.54, 0.58)	0.43 (0.41, 0.45)	0.37 (0.34, 0.39)	0.54 (0.52, 0.56)	0.33 (0.31, 0.35)	0.2 (0.17, 0.22)	0.7 (0.68, 0.71)
Well-being VAS	0.53 (0.51, 0.55)	0.41 (0.39, 0.44)	0.36 (0.34, 0.39)	0.5 (0.48, 0.52)	0.32 (0.29, 0.34)	0.21 (0.18, 0.24)	0.71 (0.7, 0.73)

* Values are the correlation (95% confidence interval). cJADAS10 = clinical Juvenile Arthritis Disease Activity Score in 10 joints; EPOCA = Epidemiology Treatment and Outcome of Childhood Arthritis; ESR = erythrocyte sedimentation rate; NAJ = number of joints with active arthritis; NLJ = number of joint with limitation on motion; PhGA = physician global assessment of overall disease activity; SJC = swollen joint count; TJC = tender joint count; VAS = visual analog scale.

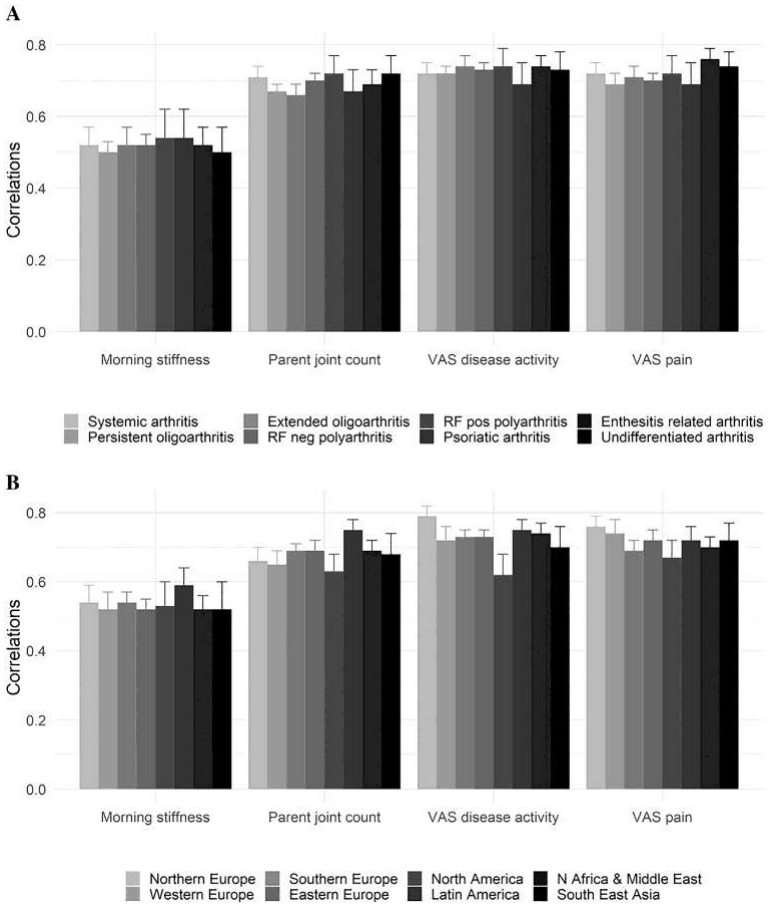

Figure 1. Comparison of Spearman's correlations of morning stiffness duration, active joint count, level of disease activity, and level of pain assessed by parents with the clinical Juvenile Arthritis Disease Activity Score in 10 joints among the International League of Associations for Rheumatology categories of juvenile idiopathic arthritis (**A**) and the different geographic areas (**B**). RF = rheumatoid factor; VAS = visual analog scale.

moderate, or high) of the patient's family (Table 3). The correlations with cJADAS10 of the 4 measures obtained from patients progressively increased from the lower age group to the higher age group (Table 3).

Reliability measurement. *Interrater reliability.* Paired data for parents and patients were available in 5,947 visits. The Spearman's correlations between the parent's and the patient's rating were 0.83 for the disease activity scale, 0.84 for the morning stiffness scale, and 0.88 for both the pain scale and the joint count. As a reference, the correlation of the well-being scale between parent's and patient's rating was 0.80.

Test–retest reliability. After a median of 7 (interquartile range 6–7) and 7 (6; 7) days from first completion, the questionnaire was filled a second time by 442 parents and 344 patients, respectively. ICCs showed almost perfect reproducibility (ICC >0.80) for all measures, with the exception of the disease activity VAS for parents' assessment (ICC = 0.78) and the well-being VAS for parents' assessment (ICC = 0.73) (Table 4).

Figure 2 presents Bland-Altman plots for each of the 4 disease activity indices, demonstrating the mean difference between measurements with 95% limits of agreement (morning stiffness 0.05 [–1.3, 1.4], joint count 0.03 [–2.9, 3.0], VAS disease activity 0.3 [–3.1, 3.7], and VAS pain 0.3 [–2.6, 3.3]) according to the baseline value. Bland-Altman plots for patients' measures are shown in Supplementary Figure 3, available on the *Arthritis Care &*

Table 3. Spearman's correlations of the parent-reported outcomes with cJADAS10 by socioeconomic status and education level and correlations of the patient-reported outcomes with cJADAS10 by age group*

	No.	Parent joint count	Morning stiffness	Pain VAS	Disease activity VAS
Socioeconomic status					
Low	1,401	0.75 (0.72, 0.78)	0.55 (0.51, 0.59)	0.78 (0.75, 0.8)	0.74 (0.71, 0.76)
Average	4,954	0.68 (0.67, 0.7)	0.52 (0.5, 0.54)	0.72 (0.7, 0.73)	0.7 (0.69, 0.72)
High	786	0.72 (0.68, 0.75)	0.53 (0.47, 0.58)	0.75 (0.71, 0.78)	0.72 (0.68, 0.76)
Education					
Elementary or lower	1,492	0.71 (0.68, 0.74)	0.52 (0.48, 0.56)	0.74 (0.72, 0.77)	0.69 (0.66, 0.72)
High school	2,823	0.71 (0.69, 0.73)	0.51 (0.48, 0.54)	0.74 (0.72, 0.76)	0.71 (0.69, 0.73)
Degree	1,790	0.71 (0.68, 0.73)	0.56 (0.52, 0.59)	0.75 (0.72, 0.77)	0.73 (0.7, 0.75)
Age group, years					
6–10	1,768	0.65 (0.62, 0.68)	0.51 (0.47, 0.55)	0.66 (0.64, 0.69)	0.69 (0.66, 0.71)
11–13	1,801	0.67 (0.64, 0.69)	0.49 (0.45, 0.53)	0.69 (0.66, 0.71)	0.7 (0.67, 0.72)
14–18	2,305	0.7 (0.67, 0.72)	0.53 (0.5, 0.56)	0.72 (0.69, 0.74)	0.73 (0.71, 0.75)
>18	114	0.73 (0.62, 0.82)	0.52 (0.37, 0.65)	0.73 (0.62, 0.81)	0.77 (0.66, 0.84)

* Values are the correlation (95% confidence interval) unless indicated otherwise. cJADAS10 = clinical Juvenile Arthritis Disease Activity Score in 10 joints; VAS = visual analog scale.

Research website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24855.

DISCUSSION

Patient self-assessment or parent proxy-assessment are nowadays considered of foremost importance in the care of chronic conditions, and in particular, of JIA, with a disease course that is mostly unpredictable. Remote patient self-assessment could foster the early recognition of disease flares, leading to timely and effective medical treatment.

This study describes the assessment of validity and reliability of 4 parent/child–reported outcomes for JIA. The choice of the 4 measures to be tested was based on the updated OMERACT core domain set for studies in JIA. In fact, 3 of these measures (pain, disease activity, and joint count) refer to domains indicated as mandatory by the OMERACT workshop, whereas stiffness is considered an important, even though optional, domain. To provide adequate strength to the validation process, the criterion validity and reliability were assessed in a large sample, including >6,000 patients from several different countries. These patients are likely to be representative of the whole spectrum of JIA phenotypes, as well as cultural background, education, and socioeconomic status. Although the patient sample was skewed toward a low level of disease activity, the EPOCA study data set was large enough to include a representative number of subjects for each disease state based on recent JADAS10 thresholds (31).

Table 4. Test–retest reliability: intraclass correlation coefficients (ICCs) of parent- and patient-reported outcomes between first and second assessment*

	No.	ICC
Parent-reported outcomes		
Parent joint count	442	0.83
Morning stiffness	442	0.86
Pain VAS	442	0.87
Disease activity VAS	442	0.78
Well-being VAS	441	0.73
Patient-reported outcomes		
Patient joint count	344	0.84
Morning stiffness	344	0.88
Pain VAS	344	0.81
Disease activity VAS	344	0.83
Well-being VAS	344	0.86

* Second assessment was performed no more than 2 weeks after first assessment. VAS = visual analog scale.

All tested measures demonstrated good criterion validity, by yielding moderate correlations with the physician-reported measures, such as PhGA and the number of joints with active arthritis, and strong correlations with the JADAS10 and cJADAS10, with the exception of morning stiffness, which remained moderately correlated with the composite disease activity scores. Correlations with cJADAS10 were similar after grouping patients by ILAR category and geographic area, suggesting that our results could be representative of different clinical settings. Furthermore, the level of correlation remained stable irrespective of the socioeconomic status of the family and the parent education level, indicating that the criterion validity of the 4 measures is not significantly affected by the social context of the family. On the other hand, the correlations with cJADAS10 of the 4 measures obtained by the patients increased in the older age group, suggesting that the higher the patient age the more reliable the parent/child–reported outcome. This finding is in line with previously reported results on the general pediatric population (32).

The 4 parent/child–reported outcomes were also found to be very reliable tools, by obtaining correlations in a strong range both in interrater and in test–retest reliability analysis. Bland-Altman plots showed 95% limits of agreement, with approximately ±3 for VAS pain, disease activity, and joint count, meaning that a difference of >3 could be interpreted as a real change, with a 5% risk of being wrong. Furthermore, the plots showed that differences between test–retest evaluations were more pronounced in the middle of the scales (almost all test–retest combinations outside

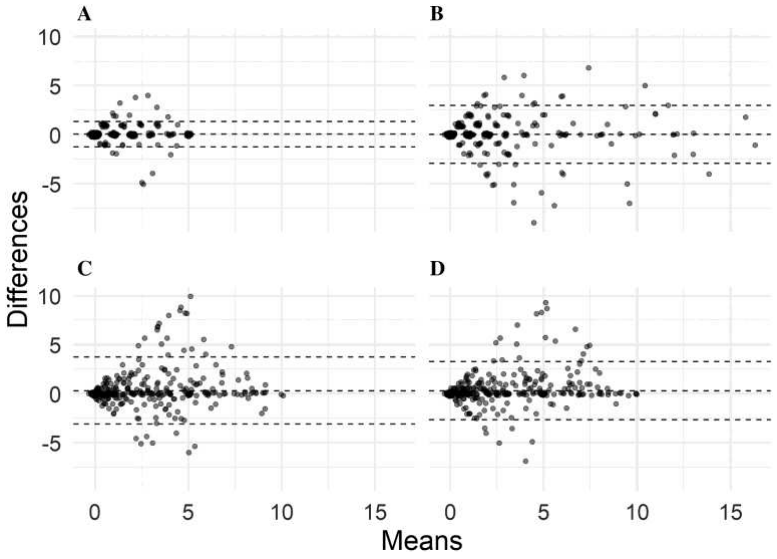

Figure 2. Agreement between scores obtained by the morning stiffness duration (**A**), parent assessment of joint count (**B**), level of disease activity by visual analog scale (VAS) (**C**), and level of pain by VAS (**D**) measures at first and second assessment illustrated by Bland-Altman plots. Interval between first and second assessment was 7 (interquartile range 6–7) days. Broken lines indicate the mean and 95% limit of agreement. Each dot represents an individual patient.

the limits of agreement occur between 2.5 and 7.5 points), whereas scores toward the lower end of the scales tended to be reproduced more accurately. Thus, parents and children deeming themselves in remission or low disease activity could report this fact trustworthily. Also, children with at least some disease activity would probably report that fact again, if asked to re-evaluate their disease activity, even though the exact score attributed to their disease activity might vary by ±3 points.

Pain perception in children with JIA is multifactorial and results from the combination of biologic, psychological, and environmental factors (11). Despite being the most common and distressful symptom of JIA, pain has been widely neglected in the development of outcome measures for JIA (33). Indeed, pain assessment is not included in the Wallace criteria for clinically inactive disease (34) or in the American College of Rheumatology Pediatric response criteria (23), which have been used as outcome measure in all the recent trials on biotechnologic drugs in JIA. Yet pain evaluation has been included in the updated core domain set for studies in JIA by OMERACT as a mandatory domain (9). The use of age-appropriate, reliable, and valid tools is recommended to assess pain in children with chronic arthritis (35). In fact, a reliable appraisal of pain in patients with JIA requires the use of well-validated pain assessment tools that could capture the multifaceted aspects of the pain experience (32). The 21-numbered circular VAS has been found to be a simpler and more feasible measure for pain self-report compared to the 100-mm VAS (28). Our study confirmed the good criterion validity of the pain 21-numbered circular VAS, which yielded strong correlations with the composite scores for disease activity JADAS10 and cJADAS10 and moderate correlations with physician-reported measures, such as the PhGA and the active joint counts. In the reliability analysis, the pain scale performed better among the 4 measures tested. Altogether, these results confirm that the 21-numbered circle is a feasible tool for pain self- or proxy-report in JIA, and its use should be encouraged both in standard clinical practice and in research settings to allow clinicians and researchers to track child pain over time.

To our knowledge, only 2 studies have investigated the role of self- or proxy-reported joint count in JIA (15,36). Even though both showed that patients and/or parents tended to overestimate the presence of arthritis when marking active joints on a manikin-format joint, Dijkstra et al found a moderate agreement between the physician and the patient total joint count. In line with that, in our analysis, both parent and patient joint count yielded moderate correlation with the number of active, swollen, and tender joint counts provided by the physician, demonstrating good criterion validity. Furthermore, parents' joint counts correlated strongly with the patient's count, and both demonstrated a very high inter-rater and retest reliability. In many instances, such as when evaluating whether treatment needs to be escalated, the exact number and location of active joints is of less importance, as long as the

overall evaluation of joint activity is in agreement between parents, patients, and physicians. This result suggests that, even though parent/patient–reported joint count cannot replace the physician's joint assessment in clinical practice, it could be helpful in JIA disease activity remote monitoring. Admittedly, the tested joint count is based on a reduced and selected list of joints as it is included in the JAMAR (20).

So far, the patient's perception of the level of disease activity in JIA has been measured through the parent/child overall well-being VAS, both in disease activity scores and in a core set of multiple criteria for the definition of different disease activity states (9,13). However, the well-being VAS measures a broader construct than the level of disease activity, including all the aspects of the disease burden affecting the patient's health-related quality of life. In this study, we provided evidence supporting the efficacy of a VAS specifically designed to assess the level of disease activity, as disease level is perceived by the patient or by caregivers. Notably, of the 2 most widely adopted disease activity scores for adults with RA, the DAS incorporates a patient global health tool (19), whereas the Simplified Disease Activity Index incorporates a patient global disease activity tool (17). Further discussion is urgently needed to identify the measure that better serves the purpose of describing the parents' or patients' perspective of the disease course. In the present study, the correlation of the disease activity scale with physician-reported measures reached greater levels compared to the overall well-being VAS. On this basis, parent and child disease activity VAS may be a suitable indicator of disease status in children with JIA, and its incorporation in the composite disease activity scores should be further investigated.

Among the 4 parent/child–reported outcomes tested, morning stiffness was the one with the lower performance in the correlation analysis, although still moderately correlated with the PhGA and the JADAS10 and highly reliable. This finding may be at least in part due to the use of a 5-point Likert scale, transformed to a 0–10 scale. Although not included in the OMERACT core-set list of mandatory variables (9), the duration of morning stiffness is included in the ACR provisional definition of inactive disease (23). Recently, some discussion has been raised on the possibility of allowing a morning stiffness duration of 15 minutes in the definition of remission, as most parents do not consider their child to be in remission in the presence of morning stiffness, even of a short duration (24).

Our results should be interpreted in the light of some potential limitations. First, multiple tools are available to measure the selected domains. Our analysis was limited to the instruments included in the JAMAR. Second, test–retest reliability was assessed with a time interval of 7–14 days between the first and second assessment. We believe this time span is appropriate to assess test–retest reliability in a chronic disease like JIA on a large scale, but we did not formally assess whether the level of disease activity was the same at the 2 time points. Another key aspect of the evaluation of outcome measures is responsiveness to change and determining minimal clinically important differences, which requires longitudinal data analysis.

In conclusion, we have provided further evidence of validity and reliability of 4 parent/child–reported outcome measures, whose referring domains are included in the OMERACT JIA core domain set. By documenting these key measurement properties, we have shown that these measures are valid instruments for patient/parents' evaluation of disease activity in JIA and are, therefore, potentially applicable not only in a research setting but also in the standard clinical care. In particular, these parent/child–reported outcomes are ideally suited to be included in a parent/patient–reported disease activity score for remote monitoring of patients.

ACKNOWLEDGMENTS

Open Access Funding provided by Universita degli Studi di Genova within the CRUI-CARE Agreement.

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 submitted for publication. Dr. Consolaro had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. van Dijkhuizen, Ridella, Naddei, Trincianti, Ruperto, Ravelli, Consolaro.

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Analysis and interpretation of data. van Dijkhuizen, Ridella, Consolaro.

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Chapter 5

Development and validation of the Parent/Patient Version of the Juvenile Arthritis Disease Activity Score

- ***Study conducted, under the mentorship of Professor Consolaro, during Dr. Naddei research fellowship at Istituto Giannini Gaslini, Genoa, Italy***
- ***Manuscript in preparation***

Introduction

Assessment of disease activity is a crucial component of the clinical management of children with juvenile idiopathic arthritis (JIA) because persistently active disease plays a major role in determining joint damage and physical functional disability. Recent treat-to-target recommendations for JIA suggest that disease activity should be assessed and documented regularly using a validated composite instrument (4), such as the Juvenile Arthritis Disease Activity Score (JADAS) (6) or its version lacking the acute phase reactant, the clinical JADAS (cJADAS), which has been found to be potentially suitable to guide a treat-to-target strategy in JIA (9, 59). Clinic visits including disease activity assessment should be scheduled every 1-3 months when treating subjects with active disease (4). However, this frequency of visits may not always be possible due to specific barriers such as geographical and health-system-related constraints and, even in the case of high-quality care, disease activity fluctuations between clinic evaluations may be underrecognized. In this scenario, the use of parent- and child-reported outcomes (PCROs) for disease activity assessment could allow a frequent remote patient monitoring, thus optimizing disease control and contributing to the success of patient care.

The incorporation of PCROs in routine assessment of children with JIA could lead to more efficient and effective clinical care, by enforcing concordance with physician's choices, improving treatment adherence, and promoting a shared decision-making strategy (15-18).

Recently, the Outcome Measures in Rheumatology (OMERACT) Working Group has recently provided a new core set of domains recommended for studies in JIA (56), empathizing the identification of parent/patient-valued domains that were underrepresented in the past JIA core set (57, 58). The domains in the OMERACT core set include both pure PCROs such as pain assessment and outcomes that are traditionally measured by the caring physician but that can be also considered for patient/parent assessment such as joint inflammatory signs (56).

The main PCROs measures for JIA have been incorporated in a multidimensional questionnaire, named Juvenile Arthritis Multidimensional Assessment Report (JAMAR), recently translated and cross-culturally validated in the national language of 49 countries (26). Although the JAMAR may be well suited to collect parent- and child-reported information in standard clinical care, it is not specifically aimed to quantify the absolute level of disease activity according to the parent or the child.

Composite scores for JIA entirely based on PCROs, named Juvenile Arthritis Parent Assessment Index (JAPAI) and Juvenile Arthritis Child Assessment (JACAI), have been developed showing good construct validity and internal consistency (60). Nevertheless, these tools also included the assessment of physical function and health-related quality of life (HRQOL) (the latter excluded in a three-item version of the scores), which can be influenced by many other factors in addition to disease activity. Disease activity composite measures totally based on patient-centered outcomes have been developed in adult rheumatoid arthritis (RA). These scores, such as the Routine

Assessment of Patient Index Data (RAPID)-3 or the RA Disease Activity Index (RADAI)-5 (61, 62), have been found to correlate strongly with the physician-driven scores of disease activity and have been successfully used to remotely monitor disease activity in RA by electronic devices (63, 64).

At present, such a measure does not exist for JIA. Developing a valid and reliable composite PCROs-based tool for remote assessment of JIA disease activity could lead to the prompt identification of JIA flares and early intervention for patients requiring treatment adjustment, and deferred appointment frequency in case of stable disease. Moreover, it could be crucial when face-to-face evaluation may be difficult or even impossible. For all those reasons, taking advantage of the initiative of the OMERACT Working Group, the purpose of the present study was to develop and validate a composite disease activity score for JIA, solely based on parent or patient-centered outcome measures, called the parent/child Juvenile Arthritis Disease Activity Score (parJADAS/childJADAS), and to provide preliminary evidence of their validity. Both the parJADAS and the childJADAS versions of the score were developed and validated.

Methods

Development of parJADAS and childJADAS

The components of the parJADAS and the childJADAS were chosen among PCROs which referring domains are included in the updated OMERACT core domain set for studies in JIA (56). Briefly, the OMERACT is an independent initiative of international stakeholders, including health professionals, methodologists, and patient research partners, interested in outcome measurement in rheumatology. In the process leading to the development of the new core domain set, JIA patients, their parents, and parents' associations other than clinicians and researchers contributed substantially to the

identification and ranking of the most relevant disease domains which referred to physician-reported measures, PCROs, or laboratory exams (56, 58). Consensus methods and selection of domains procedure have been described in detail (56). The parJADAS and the childJADAS include the following 4 items: parent/patient assessment of disease activity, pain intensity level, active joint count, and morning stiffness (MS). Three of these measures (pain, disease activity and joint count) refer to domains indicated as mandatory by the OMERACT workshop. In fact, "pain" and "joint inflammatory signs/active joints" obtained the highest ranking after OMERACT core domain set consensus voting among the domains that can be assessed by a parent/patient reported measure. "Patient's perception of disease/overall well-being" was also highly ranked by both physicians and parents and patients. MS has been considered an important, even though optional, domain by OMERACT workshop.

The four measures included in the parJADAS and the childJADAS, which are incorporated in the JAMAR (26), have been recently showed to be valid and reliable tools for patient monitoring (52).

The level of child's disease activity was rated on a 21-numbered circle scale (0 = no activity; 10 = maximum activity), responding to the question "Considering all the symptoms, such as pain, joint swelling, morning stiffness, fever (if due to arthritis), and skin rash (if due to arthritis), please evaluate the level of activity of your child's illness at the moment". The question was adapted for patient's self-assessment.

The intensity of child's pain was rated on a 21-numbered circle scale (0 = no pain; 10 = extreme pain) (28), responding to the question "How much pain has your child had because of the illness over the past week?". The question was adapted for patient's self-assessment.

In the JAMAR, happy and sad faces drawings were added to the anchor words at the 2 extremes of both disease activity and pain visual analogue scale, because in preliminary testing some assessors misinterpreted the score rule by interpreting the score 10 as the best and the score 0 as the worst. After adding the faces, misinterpretation was no longer observed (20).

The proxy- or self-assessment of joint disease was obtained by asking the parent or the child to rate the presence of pain or swelling in the following joints or joint groups: cervical spine, lumbo-sacral spine, shoulders, elbows, wrists, small hand joints, hips, knees, ankles, and small foot joints. The active joint count was cut to a maximum of 10 joints.

For the evaluation of MS, the parent (or the child) was asked whether MS was absent (0 points) or present. If present, its duration was measured with a 5-point Likert scale, ranging from 2 to 10, with the following anchors: “Less than 15 minutes”, “15 to 30 minutes”, 30 minutes to 1 hour”, “1 to 2 hours”, and “More than 2 hours”.

The parJADAS and the childJADAS were calculated as the simple linear sum of the scores of its 4 components, which yields a global score of 0–40.

Study datasets

Two multinational samples composed of patients meeting the International League of Associations for Rheumatology (ILAR) criteria for JIA (1) were used to validate the parJADAS and the childJADAS.

To assess parJADAS and childJADAS construct validity, discriminant ability, and internal consistency, a dataset of 9,081 subjects with JIA from 49 countries enrolled in the Epidemiology, treatment and Outcome of Childhood Arthritis (EPOCA) study was used (65). Briefly, the EPOCA study is a survey conducted by the Paediatric

Rheumatology International Trials Organisation (PRINTO) between 2011 and 2016. Each participating centre was asked to enroll 100 patients with JIA that were seen consecutively over 6 months or, if the centre did not expect to see at least 100 patients within 6 months, to enroll all patients seen consecutively within the first 6 months after study start. For each visit, retrospective and cross-sectional data were collected, including both physician-centered data and the PCROs incorporated in the JAMAR, filled by a legal guardian and, when appropriate, by the patient. The demographic and clinical features of these patients have been reported elsewhere (65). Data from 8,431 parents and 5,873 children who had all the variables included in the parJADAS and the childJADAS available were retained (table 1). For the purpose of analysis, children with systemic arthritis, rheumatoid factor (RF)-positive and -negative polyarthritis or extended oligoarthritis were included in the polyarthritis group. The oligoarthritis group included children with persistent oligoarthritis. Based on the average number of active joints ($\leq$2 or >2, respectively), children with enthesitis-related arthritis or undifferentiated arthritis were assigned to the oligoarthritis group, while patients with psoriatic arthritis to the polyarthritis group.

Predictive ability and responsiveness to change were assessed using a longitudinal dataset of subjects enrolled in the PharmaChild Registry, an observational multinational registry to assess the long-term safety and efficacy of medications including over 8,200 children with JIA.

In both EPOCA study and Pharmachild registry, the JAMAR including the four PCROs of the parJADAS and the childJADAS was proposed for filling to a caregiver (proxy-reported measure) and to the patient when he/she was deemed by the caring physician able to understand and respond to the questions in the questionnaire (self-reported measures). In some instances, the JAMAR was filled only by the patient.

All participating centers to EPOCA study and PharmaChild registry obtained approval from their respective ethics committee and consent/assent from parents/patients based on existing national regulations.

Validation procedures

Validation of the parJADAS and the childJADAS was based on evaluation of construct validity, internal consistency, discriminant and predictive ability, and responsiveness to change. While construct validity, internal consistency, and discriminant ability were calculated distinctly for parJADAS and childJADAS, predictive ability and responsiveness to change were assessed only for the parJADAS, because the amount of patients' observation in the corresponding dataset was not sufficient.

Construct validity is a form of validation that seeks to examine whether the construct in question, in this case the parJADAS and the childJADAS, is related to other measures in a manner consistent with a priori prediction. Given that the parJADAS and the childJADAS were devised to measure JIA activity, we expected moderate to high correlations with the measures more closely related to disease activity, such as swollen, tender, and active joint counts and physician global assessment (PGA) on a 0-10 VAS. We also predicted parJADAS and the childJADAS to be highly correlated with the parent/patient rating of child's overall well-being on a 21-numbered circle VAS, which showed strong correlations with JIA activity outcome measures (20). High correlations with the JADAS10 and the clinical JADAS10 (cJADAS10) (6, 9) were also predicted, since these composite scores of disease activity include the parent/patient well-being VAS. Correlation with restricted joint count was predicted to be low to moderate because this measure combines the effect of both disease activity and damage. It is known that PCROs poorly correlate with acute-phase reactants (24), therefore a low correlation

between parJADAS and the childJADAS and ESR was expected. Moreover, parJADAS and the childJADAS was correlated with the Juvenile Arthritis Functionality Scale (JAFS) which assesses the functional ability (24), and with the HRQOL assessment by the Pediatric Rheumatology Quality of Life Scale (PRQOL) (25) including two subdimensions, physical health (PhHQOL) and psychosocial health (PsHQOL) quality of life. In these cases, no prediction was attempted, because functional ability and HRQOL are multidimensional concepts that can be affected by several other factors in addition to disease activity. To assess the impact of socio-economic status and parent education on the parJADAS, the above-mentioned correlations were also computed after grouping patients by family socio-economic status (subjectively rated by the attending physician as low, average or high), and by parent education level (elementary or lower, high school or degree). All correlations were calculated using Spearman's rank statistics and were considered high, moderate, or poor when >0.7, 0.4–0.7, or <0.4, respectively (66).

Discriminant ability was assessed in the EPOCA dataset by comparing absolute scores of parJADAS and the childJADAS in patients judged as being in remission, continued activity, or disease flare by the caring physician and in patients with a symptom state considered satisfactory or not by parents (or by children themselves for the childJADAS) (67). Moreover, the parJADAS and the childJADAS scores were compared in subjects classified in remission or not according to the Wallace criteria (37) and in patients categorized into different disease activity state groups according to the American College of Rheumatology (ACR) 2021 cJADAS-10 cut-offs (68): inactive disease (ID), minimal active disease (MiDA), moderate active disease (MoDA) and high active disease (I). To assess the influence of damage on the parJADAS and the childJADAS, the score levels were compared in subjects in remission according to the Wallace criteria (37) and

with more than 3 years of disease course with or without damage according to the Juvenile Arthritis Damage Index (JADI) (69). Comparisons of absolute scores among the groups were made by Mann-Whitney U test or Kruskal-Wallis test, as appropriate.

The internal consistency of the parJADAS and the childJADAS was determined by calculating Cronbach's alpha coefficient (70) and 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 (71).

An exploratory factor analysis (EFA) was conducted on the 4 items of the parJADAS and the childJADAS in order to examine the internal structure. The factors were extracted according to the principal factors method and the optimal number of factor extraction was based upon eigenvalues ≥ 1, further inspection of the corresponding scree plot. The factors were rotated by the varimax method.

To assess predictive ability of parJADAS, patients enrolled in the PharmaChild were retained if they had 2 years of follow up and at least 4 visits with parJADAS available during the first year since enrolment (n=332). The area under curve (AUC) (figure 1) of the parJADAS in the first year of PharmaChild registry participation was calculated and compared in subjects with or without reduced functional ability (JAFS=0 or JAFS>0, respectively) at 2 years and in subjects who achieved or did not achieve clinically ID at 2 years. Comparison of AUCs was made by Mann-Whitney U test.

Responsiveness to change was assessed by computing the standardized response mean (SRM) (72) in a subgroup of JIA patients included in the PharmaChild registry. Subjects were included if they had a study visit at the time of biologic treatment initiation and a subsequent consecutive study visit no more than 6 months after biologic treatment initiation, with a subjective rating of improvement by the attending physician. SRM was computed by dividing the absolute mean change of the parJADAS between first and

second visit by the standard deviation of the change. According to Cohen (73), the threshold levels for SRM were defined as follows: ≥0.20 = small, ≥0.50 = moderate , ≥0.80 = good.

All statistical tests were 2-sided; a p-value < 0.05 was considered statistically significant. Rstudio Team (2020, version: 1.3.1093) was used to conduct the statistical analysis.

Results

Construct validity

The Spearman's correlation coefficients used to assess construct validity of the parJADAS are summarized in Table 2. As predicted, the parJADAS was correlated at a high level with the composite scores of disease activity, the JADAS-10 and the cJADAS-10, and with the well-being VAS. Also as expected, parJADAS correlated moderately with those physician-centered outcome measures closely related to disease activity, such as swollen, tender, and active joint counts and with the PGA. Correlation with restricted joint count resulted also moderate, even though at a lower level. As predicted, parJADAS correlation with the ESR was in the low range. Finally, correlations with the outcome measures related to functional ability and quality of life were found to be moderate-to-high.

The level of correlation of the parJADAS with the other JIA outcome measures remained stable after grouping patients by socio-economic status or parent education level, except for correlation with ESR which resulted in moderate range in patients with a lower socio-economic status or parent education level (table 3 and 4). Moreover,

slightly higher correlations with PGA and JAFS were found in patients with a low socio-economic level (table 3).

Correlations of childJADAS with the other measures were in same range of the parJADAS, except for the correlation with restricted joint count resulting poor (table 2).

Internal consistency

Chronbach's alpha value was calculated to measure the internal consistency of the parJADAS and childJADAS, resulting substantial in both cases (0.85 and 0.83, respectively). Removal of individual items of parJADAS one at a time decreased internal consistency, whereas the removal of morning stiffness led to a minimal increase of the childJADAS Chronbach's alpha value from 0.83 to 0.84.

With respect to the EFA, the Kaiser–Meyer–Olkin (KMO) measure was 0.79 indicating that the sample available for the parents was adequate, and this result was confirmed from the Bartlett's Test of Sphericity ($p<0.0001$) indicating that a factor analysis may be useful. Same results were obtained analyzing the children's sample (KMO=0.78, Bartlett's Test of Sphericity ($p<0.0001$). The EFA suggested that one factor explained 59.0% of the variance in the parent sample and 61.0% in the child sample, as confirmed by the corresponding scree plot (Figure 2a/2b).

The factor loadings were high for both the samples: they ranged from 0.60 (active joint count and MS) to 0.90 (parent/patient assessment of disease activity, pain intensity level) (table 5), indicating that the 4 items work well together.

Discriminant ability

Both the parJADAS and the childJADAS revealed strong ability to discriminate patients categorized subjectively in different disease activity states by the attending physician

(Fig. 3a/3b, p<0.0001), in patients in with a symptom state judged acceptable or not by parent or child (Fig. 4a/4b, p<0.0001), and in patients with active or inactive disease according to the Wallace criteria (Fig. 5a/5b, p<0.0001). The parJADAS and the childJADAS also discriminated well among patients with different states of disease according to the cJADAS10 (fig. 6a/6b, p<0.0001).

When assessing the influence of damage on parJADAS and childJADAS, we found that the two scores' levels were not different in inactive patients with more than 3 years of disease duration with or without damage by JADI (fig. 7a/7b, p=0.75 and p=0.41).

Median values and interquartile ranges of parJADAS and childJADAS among the different groups of patients are reported in table 6.

Predictive ability

Figure 1 shows the parJADAS AUC of a patient during the first year of PharmaChild registry participation. Subjects in remission at 2-year follow-up had smaller parJADAS AUC in the first year compared to patients with active disease (0.5 [0.0, 2.1] vs 2.9 [0.4, 2.1], p <0.001). Patients with impaired physical function (N=119 with JAFS>0) at the 2-year follow-up had greater parJADAS AUC in the first year compared to patients with normal physical function (N=132) (4.5 [0.1, 1.6] vs 0.5 [0.1, 1.6], p<0.001). These data indicate very good predictive ability of the parJADAS.

Responsiveness to change

In the PharmaChild registry, 60 patients (29 RF-negative polyarthritis, 11 systemic arthritis patients) met the requirements for SRM analysis. Second visit was at a median

of 37 days (I-III quartile: 28-95 days) after biologic treatment initiation. The SRM value obtained was 0.71.

Discussion

This study describes the development and the validation of a new patient/parent-centered composite disease activity score for JIA. This score combines information from level of child's disease activity, rating of pain intensity, parent/patient joint count and duration of morning stiffness into a continuous measure.

The choice of the measures to be incorporated in the parJADAS and the childJADAS was based on the updated OMERACT core domain set for studies in JIA. Three of the selected four PCROs (child's disease activity, pain intensity, parent/patient joint count) are related to domains indicated as mandatory by the OMERACT workshop, whereas stiffness is considered an important, even though optional, domain (56). We have recently provided further evidence of the validity and reliability of each of those four measures, showing that they are ideally suited for the remote assessment of disease course and, therefore, for the incorporation in a PCROs-based composite score for disease activity (52). Altogether, these processes ensure the face and content validity of the parJADAS and the childJADAS.

The score of the parJADAS and the childJADAS results from the arithmetic sum of the scores of each individual component, which makes its calculation simple and quick. The disease activity and pain ratings are both measured on a 21-numbered circle VAS from 0 to 10. To give equal weight to all measures included in the index, MS score also ranges from 0 to 10 depending on MS presence and duration and active joint count by parent/patient is cut to a maximum of 10 joints.

To provide adequate strength to the validation process, the construct validity, discriminant and predictive ability, internal consistency, and responsiveness to clinical change of the scores were assessed using two patient samples including more than 8,500 subjects from several different countries. These patients are likely to be representative of the whole spectrum of JIA phenotypes and severity.

Both the parJADAS and the childJADAS demonstrated good construct validity by yielding strong correlations with the JADAS and fair correlations with physician driven outcome measures, such as the PGA and the active joint count. This suggests that the parJADAS and the childJADAS may serve as a surrogate of physician's evaluations. Correlations of the parJADAS remained similar after grouping patients by family socio-economic status and parent education level, suggesting that the family social or cultural background does not affect the construct validity of the score.

Both the parJADAS and the childJADAS proved able to distinguish well between diverse states of disease according to the opinion of the caring physician or the parent/patients themselves. Moreover, both indices discriminated well between different states of disease activity defined as per Wallace criteria (37) or the new ACR 2021 cJADAS10 cut-offs (68), showing an excellent discriminant ability in capturing the diverse levels of disease activity. On the other hand, the level of parJADAS and the childJADAS resulted similar in inactive patients with or without damage, indicating that the presence of damage does not influence the parJADAS and the childJADAS when there is no active disease. That the childJADAS performed similarly to the parJADAS suggests that children are acceptable self-assessor of their disease status.

Evidence of the excellent predictive ability of the parJADAS was demonstrated by the fact that the AUC of the parJADAS during the first year of PharmaChild registry

participation predicted disease outcome in terms of functional ability and achievement of inactive disease at 2-year follow-up.

Evaluation of internal consistency yielded satisfactory results, with the Cronbach's alpha coefficient resulting substantial for both indices. Responsiveness to change over time was in line with the expectations, with a SRM in moderate range in patients judged as improved by the caring physician after starting a bDMARD.

Our study should be interpreted in light of some potential limitations. Although domains included in the parJADAS and in the childJADAS were selected among those highly rated by different stakeholders in the process leading to the development of the OMERACT JIA core domain set, the tools to measure these domains were selected among those available in the JAMAR questionnaire. In particular, the tool to assess joint signs of inflammation includes a selected count of joints and joint group which does not consider temporomandibular joints. However, this tool was recently fully validated (52) and it is the only available tool for parent/patient self-assessment of joint inflammatory signs.

In conclusion, we have developed a new parent/child centered disease activity score for JIA, which is based on the simple arithmetic sum of 4 clinical measures. The instrument was found to be feasible and to possess both face and content validity; furthermore, it exhibited good construct validity, discriminant and predictive ability, internal consistency, and responsiveness to clinical change in a large patient population. By documenting these key measurement properties, we have shown that the parJADAS and the childJADAS is a valid instrument for the parent/patient assessment of disease activity in JIA and is, therefore, potentially applicable not only in research settings but also in the standard clinical care. A regular home-completion of parJADAS and the childJADAS through electronic devices could be used for the remote assessment of the

disease activity, therefore filling the yet unmet need for more frequent patient monitoring in JIA to improve disease management and potentially reduce the burden on clinic time.

Tables

Table 1. Main demographic and clinical features of the EPOCA sample.

	EPOCA Parents		**EPOCA Children**	
Females (%)	N=8,431	5,606 (66.5)	N=5,873	3,841 (65.4)
Age at onset (median [IQR])	N=8,425	5.4 [2.4, 9.6]	N=5,870	7.4 [3.7, 10.8]
Age at visit (median [IQR])	N=8,431	11.4 [7.4, 14.6]	N=5,873	13.1 [10.5, 15.5]
Disease duration (median [IQR])	N=8,430	3.8 (1.7, 6.8)	N=5,873	4.8 (2.3, 7.9)
ILAR category (%)	N=8,431		N=5,873	
Sistemic arthritis		914 (10.8)		601 (10.2)
Persistent oligoarthritis		2,666 (31.6)		1,529 (26)
Extended oligoarthritis		910 (10.8)		686 (11.7)
RF-negative polyarthritis		1,969 (23.4)		1,425 (24.3)
RF-positive polyarthritis		352 (4.2)		323 (5.5)
Psoriatic arthritis		277 (3.3)		217 (3.7)
Enthesitis related arthritis		861 (10.2)		794 (13.5)
Undifferentiated arthritis		482 (5.7)		298 (5.1)
Socio-economic status (%)	N=6,954		N=4,853	
Low		1,364 (19.6)		991 (20.5)
Average		4,815 (69.2)		3,324 (68.7)

High		775 (11.1)		520 (10.8)
Education (%)	N=5,957		N=4,095	
Elementary or lower		1,447 (24.3)		1,081 (26.4)
High school		2,742 (46)		1,907 (46.6)
Degree		1,768 (29.7)		1,107 (26.9)
PGA VAS (median [IQR])	N=8,429	1.00 [0.0, 3.0]	N=5,873	1.00 [0.0, 3.0]
Swollen joint count (median [IQR])	N=8,430	0.0 [0.0, 1.0]	N=5,873	0.0 [0.0, 1.0]
Tender joint count (median [IQR])	N=8,430	0.0 [0.0, 1.0]	N=5,873	0.0 [0.0, 2.0]
Restricted joint count (median [IQR])	N=8,430	0.0 [0.0, 2.0]	N=5,873	0.0 [0.0, 2.0]
Active joint count (median [IQR])	N=8,430	0.0 [0.0, 2.0]	N=5,873	0.0 [0.0, 2.0]
ESR (median [IQR])	N=6,537	10.0 [5.0, 20.0]	N=4,604	10.0 [5.0, 20.0]
Well-being VAS (median [IQR])	N=8,403	1.0 [0.0, 3.5]	N=5,854	0.5 [0.0, 3.5]
JADAS10	N=6,512	3.5 [0.5, 9.0]	N=4,589	3.5 [0.5, 9.0]
cJADAS10	N=8,402	3.0 [0.5, 8.0]	N=5,854	3.5 [0.5, 8.0]
Pain VAS (median [IQR])	N=8,431	1.0 [0.0, 3.5]	N=5,873	1.0 [0.0, 3.5]
Disease activity VAS (median [IQR])	N=8,431	1.0 [0.0, 3.5]	N=5,873	0.5 [0.0, 3.5]
parent/child joint count (median [IQR])	N=8,431	1.0 [0.0, 2.0]	N=5,873	1.0 [0.0, 2.0]
MS duration (median [IQR])	N=8,431	0.0 [0.0, 2.0]	N=5,873	0.0 [0.0, 1.0]
par/childJADAS (median [IQR])	N=8,431	4.0 [0.0, 12.0]	N=5,873	3.5 [0.0, 11.0]

IRQ = interquartile range; ILAR = International League of Associations for Rheumatology; RF = Rheumatoid factor; PGA = physician global assessment of disease activity; VAS = visual analogue scale; ESR = erythrocyte sedimentation rate; MS = Morning stiffness; JADAS10 = Juvenile Arthritis Disease Activity Score 10; cJADAS10

= clinical Juvenile Arthritis Disease Activity Score 10; par/childJADAS: parent/child Juvenile Arthritis Disease Activity Score.

Table 2. Spearman's correlations between the parJADAS/childJADAS and other JIA outcome measures.

Outcome measures	parJADAS		childJADAS	
	No. of patients	Spearman Rho*	No. of patients	Spearman Rho*
ESR	6,537	0.25	4,604	0.23
Restricted joint count	8,430	0.41	5,873	0.38
PsHQOL score	8,213	0.47	5,873	0.48
Swollen joint count	8,430	0.47	5,873	0.45
Active joint count	8,430	0.53	5,873	0.52
Tender joint count	8,430	0.59	5,873	0.59
PGA VAS	8,430	0.64	5,873	0.63
JAFS	8,353	0.67	5,873	0.69
PhHQOL score	8,301	0.75	5,873	0.77
JADAS10	6,512	0.78	4,589	0.76
Well-being VAS	8,403	0.78	5,854	0.78
cJADAS10	8,402	0.78	5,854	0.77

ESR = erythrocyte sedimentation rate; PsHQOL = psychosocial health quality of life; PGA = physician global assessment of disease activity; VAS = visual analogue scale; JAFS = Juvenile Arthritis Functionality Scale; PhHQOL = physical health quality of life; JADAS10 = Juvenile Arthritis Disease Activity Score 10; cJADAS10 = clinical Juvenile Arthritis Disease Activity Score 10. *p-value <0.0001 for all comparisons.

Table 3. Spearman's correlations between the parJADAS and other JIA outcome measures after grouping patients by socio-economic status (subjectively rated by the attending physician as low, average or high).

Outcome measures	Socioeconomic status	No. of patients	Spearman Rho*
ESR	Low	1,124	0.45
	Average	3,812	0.23
	High	580	0.28
Restricted joint count	Low	1,364	0.49
	Average	4,814	0.41
	High	775	0.47
PsHQOL score	Low	1,336	0.48
	Average	4,741	0.45
	High	748	0.41
Swollen joint count	Low	1,364	0.55
	Average	4,814	0.48
	High	775	0.52
Active joint count	Low	1,364	0.64
	Average	4,814	0.53
	High	775	0.6
Tender joint count	Low	1,364	0.6
	Average	4,814	0.57
	High	775	0.59
PGA VAS	Low	1,364	0.71
	Average	4,813	0.63
	High	775	0.66
JAFS	Low	1,347	0.72
	Average	4,773	0.66
	High	769	0.63
PhHQOL score	Low	1,347	0.77
	Average	4,741	0.75
	High	758	0.72
JADAS10	Low	1,122	0.83
	Average	3,797	0.77
	High	576	0.79
Well-being VAS	Low	1,360	0.81

	Average	4,800	0.76
	High	771	0.77
cJADAS10	Low	1,122	0.83
	Average	4,799	0.77
	High	771	0.81

ESR = erythrocyte sedimentation rate; PsHQOL = psychosocial health quality of life; PGA = physician global assessment of disease activity; VAS = visual analogue scale; JAFS = Juvenile Arthritis Functionality Scale; PhHQOL = physical health quality of life; JADAS10 = Juvenile Arthritis Disease Activity Score 10; cJADAS10 = clinical Juvenile Arthritis Disease Activity Score 10. *p-value <0.0001 for all comparisons.

Table 4. Spearman's correlation between the parJADAS and other JIA outcome measures after grouping patients by parent education level (elementary or lower, high school or degree)

Outcome measures	**Educational level**	**No. of patients**	**Spearman Rho***
ESR	Elementary or lower	1,200	0.43
	High school	2,168	0.25
	Degree	1,378	0.26
Restricted joint count	Elementary or lower	1,447	0.46
	High school	2,742	0.43
	Degree	1,768	0.43
PsHQOL score	Elementary or lower	1,409	0.46
	High school	2,673	0.46
	Degree	1,722	0.43
Swollen joint count	Elementary or lower	1,447	0.49
	High school	2,742	0.5
	Degree	1,768	0.5
Active joint count	Elementary or lower	1,447	0.57
	High school	2,742	0.56
	Degree	1,768	0.57
Tender joint count	Elementary or lower	1,447	0.62
	High school	2,742	0.59

	Degree	1,768	0.58
PGA VAS	Elementary or lower	1,447	0.69
	High school	2,742	0.66
	Degree	1,767	0.65
JAFS	Elementary or lower	1,429	0.68
	High school	2,720	0.66
	Degree	1,752	0.66
PhHQOL score	Elementary or lower	1,428	0.75
	High school	2,706	0.75
	Degree	1,737	0.75
JADAS10	Elementary or lower	1,194	0.81
	High school	2,160	0.78
	Degree	1,374	0.79
Well-being VAS	Elementary or lower	1,441	0.79
	High school	2,731	0.78
	Degree	1,763	0.77
cJADAS10	Elementary or lower	1,441	0.8
	High school	2,731	0.79
	Degree	1,763	0.79

ESR = erythrocyte sedimentation rate; PsHQOL = psychosocial health quality of life; PGA = physician global assessment of disease activity; VAS = visual analogue scale; JAFS = Juvenile Arthritis Functionality Scale; PhHQOL = physical health quality of life; JADAS10 = Juvenile Arthritis Disease Activity Score 10; cJADAS10 = clinical Juvenile Arthritis Disease Activity Score 10. *p-value <0.0001 for all comparisons.

Table 5. Results of factorial analysis on the items of parJADAS and childJADAS.

	parJADAS	childJADAS
Variance explained by the factor, %	59	61
Item loadings		
Pain VAS	0.89	0.9
Disease activity VAS	0.83	0.9
MS	0.66	0.63
Joint count	0.66	0.65

parJADAS: parent Juvenile Arthritis Disease Activity Score; childJADAS: child Juvenile Arthritis Disease Activity Score; VAS = visual analogue scale; MS = Morning stiffness.

Table 6. Discriminant ability of parJADAS and childJADAS

	Disease state by physician			
	Remission	**Continued activity**	**Flare**	**p-value**
parJADAS (median [IQR])	0.5 [0.0, 3.5]	9.0 [3.5, 17.0]	12.0 [5.5, 20.0]	<0.0001
n	4,160	3,273	906	
childJADAS (median [IQR])	0.5 [0.0, 3.0]	8.0 [3.0, 15.0]	11.5 [5.0, 17.0]	<0.0001
n	2,898	2,365	609	
	Symptom state by parent/child (67)			
	Acceptable		**Not Acceptable**	**p-value**
parJADAS (median [IQR])	1.5 [0.0, 7.0]		13.0 [6.5, 20.5]	<0.0001
n	2,461		5,922	
childJADAS (median [IQR])	1.0 [0.0, 5.5]		11.0 [5.0, 17.5]	<0.0001
n	3,850		1,977	
	Inactive disease by Wallace criteria (37)			
	Yes		**No**	**p-value**
parJADAS (median [IQR])	0.0 [0.0, 1.5]		8.0 [2.0, 15.5]	<0.0001
n	2,689		5,742	

childJADAS (median [IQR])	0.0 [0.0, 1.5]		6.5 [2.0, 14.0]		<0.0001
n	1,791		4,082		
	Disease state by cJADAS10§ (68)				
	ID	**MiDA**	**MoDA**	**HDA**	**p-value**
parJADAS (median [IQR])	0.0 [0.0, 2.0]	4.0 [1.0, 8.0]	11.5 [6.0, 17.0]	21.0 [15.0-27.0]	<0.0001
n	3,595	1,473	2,604	730	
childJADAS (median [IQR])	0.0 [0.0, 2.0]	3.0 [1.0, 7.0]	10.0 [5.0, 15.0]	18.0 [13.5-23.6]	<0.0001
n	2,457	1,044	1,829	524	
	Damage by JADI* (69)				
	No damage		**Damage**		**p-value**
parJADAS (median [IQR])	0.0 [0.0, 1.5]		0.0 [0.0, 1.5]		0.75
n	1,450		292		
childJADAS (median [IQR])	0.0 [0.0, 1.5]		0.0 [0.0, 1.0]		0.41
n	1,133		232		

parJADAS = parent Juvenile Arthritis Disease Activity Score; IRQ = interquartile range; childJADAS = child Juvenile Arthritis Disease Activity Score; cJADAS-10 = clinical Juvenile Arthritis Disease Activity Score 10; ID = inactive disease; MiDA = minimal disease activity; MoDA = moderate disease activity; HDA = high disease activity; JADI = Juvenile Arthritis Damage Index.
§According to the American College of Rheumatology 2021 cJADAS10 cut-offs (68).
*Only in inactive patients according to Wallace criteria with more than 3 year of disease duration.

Figures

Figure 1. Area Under the Curve of the parJADAS of a patient during the first year of PharmaChild registry participation. Subjects with active disease and with impaired physical function at 2-year follow-up (red dashed line) had greater parJADAS AUC in the first year of registry participation compared to patients with inactive disease and with normal physical function, respectively.

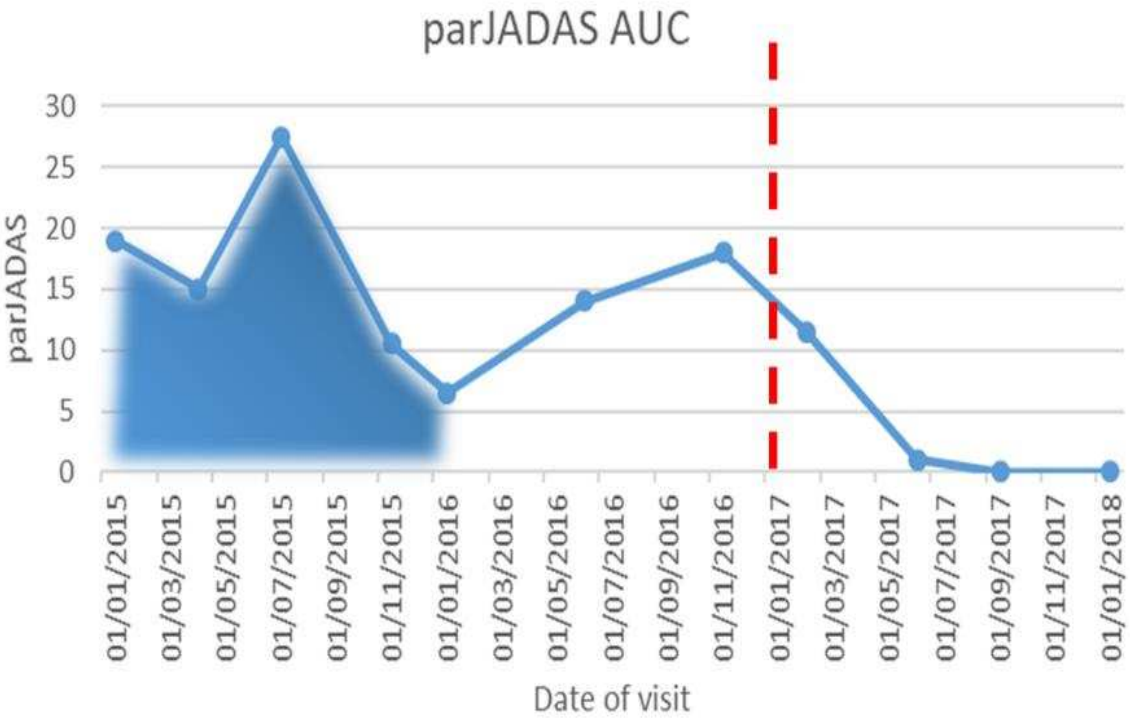


Figure 2. Plot showing factor analysis of the four items included in the parentJADAS (2a) and in the childJADAS (2b).

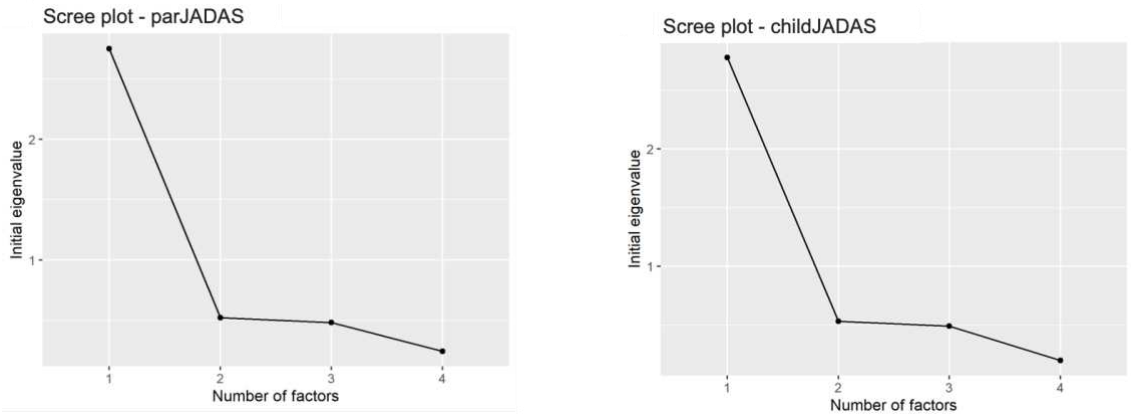


Figure 3. Comparison by Kruskal-Wallis test of the level of parJADAS (3a) and childJADAS (3b) in patients judged in remission, continued activity and flare by the caring physician.

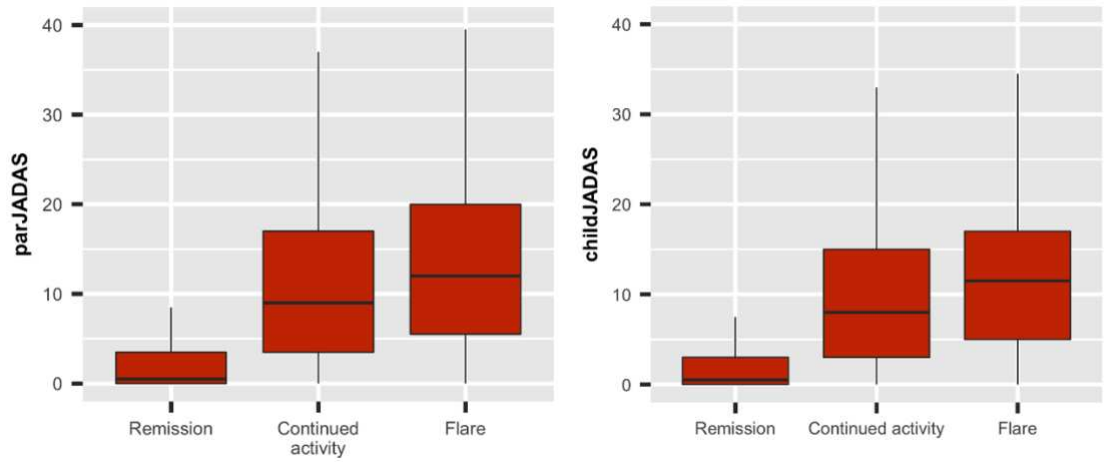


Figure 4. Comparison by Mann-Whitney U test of parJADAS (4a) and childJADAS (4b) values between patients with a symptom state judged acceptable or not by the parent and the child.

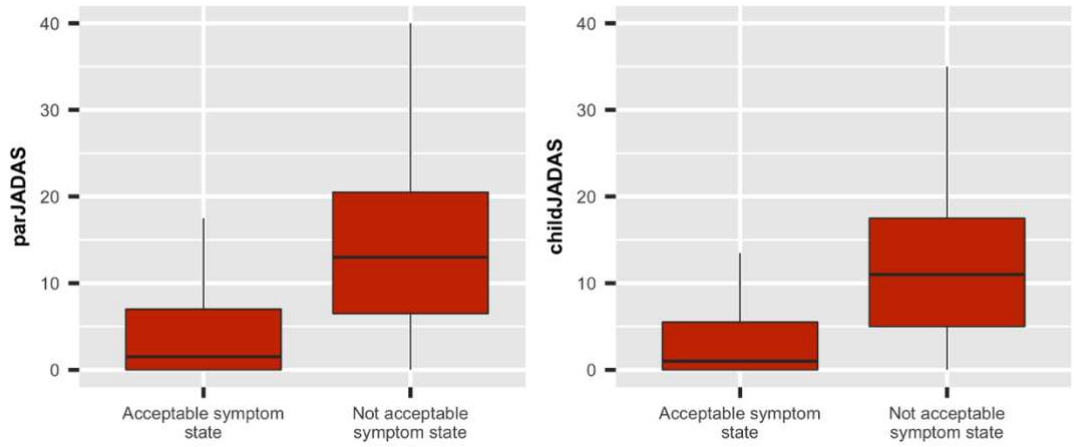


Figure 5. Comparison by Mann-Whitney U test of parJADAS (5a) and childJADAS (5b) values between patients with active and inactive disease by Wallace criteria (37).

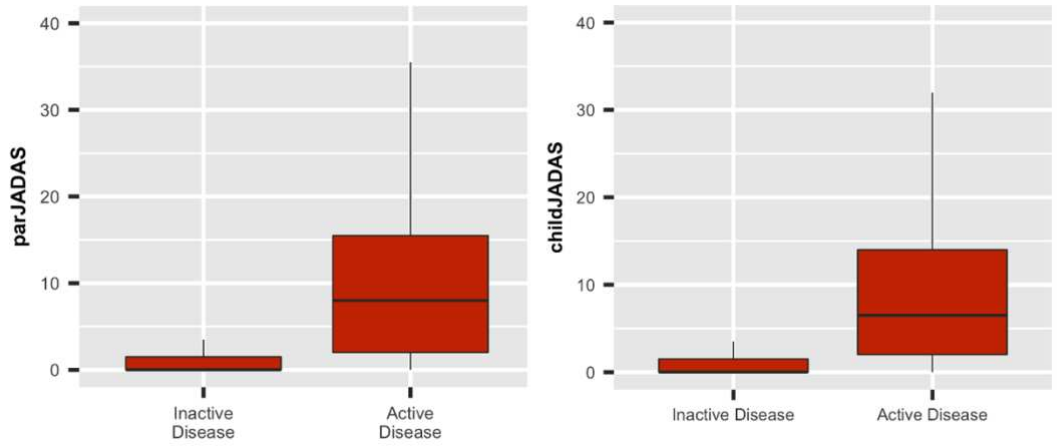


Figure 6. Comparison by Kruskal-Wallis test of the level of parJADAS (6a) and childJADAS (6b) among patients with clinical JADAS10–based inactive disease (ID), those with minimal disease activity (MiDA), those with moderate disease activity (MoDA), and those with high disease activity (HDA).

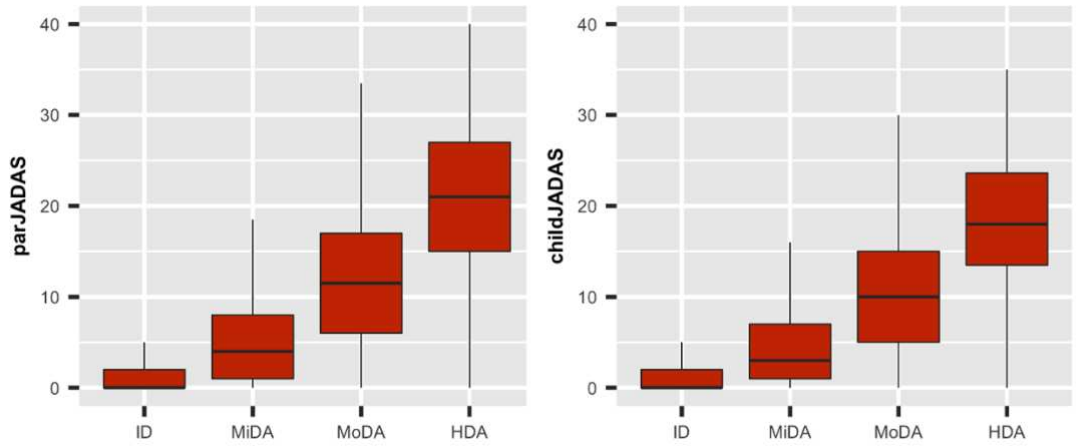
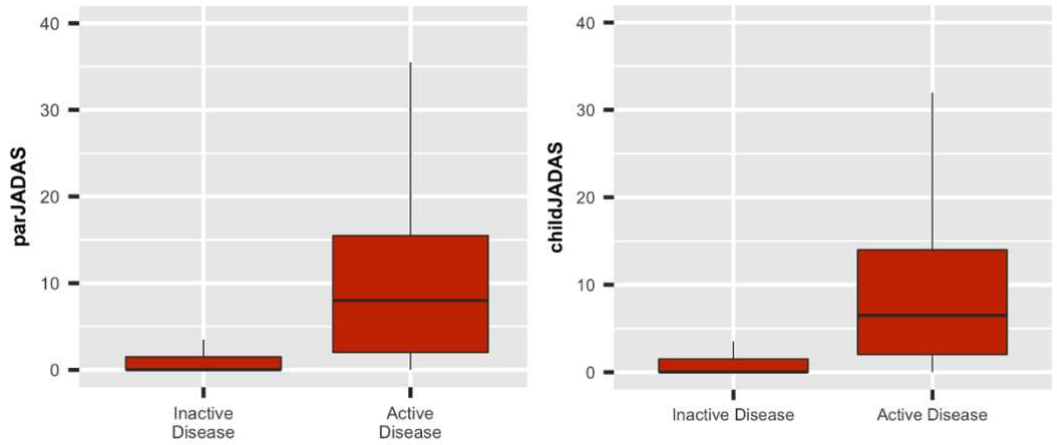


Figure 7. Comparison by Mann-Whitney U test of the level of parJADAS (7a) and childJADAS (7b) in inactive patients with or without damage according to the JADI, with more than 3 years of disease course active and inactive disease state according to Wallace criteria (37).



Chapter 6

Conclusive remarks

The regular assessment of disease activity through validated and reliable tools is of utmost importance in the management of patients with juvenile idiopathic arthritis (JIA). The treatment target and the therapeutic plan should be based on shared decisions between the parent/patient and the physician (4). Patient/parent reported outcome measures (PCROs) provide a direct insight on the parent's and child's perceptions of disease course and effectiveness of therapeutic interventions. The incorporation of PCROs in the routine assessment of children with JIA may lead to more efficient and effective clinical care, by enforcing concordance with physician's choices (15-18). The identification of valid and reliable PCROs could be crucial to remotely monitor disease activity when in-face evaluation is not possible, as happened during Coronavirus Disease 2019 (COVID-19) pandemic (19) and reported in the chapter 2 of this thesis.

Against this scenario, our research was aimed to develop a new tool, solely based on PCROs, for the assessment of disease activity by parent/patient. First, to identify the items suitable to be included into this new tool, we analyzed the measurement properties of following 4 PCROs for disease activity: 1) parent's or child's assessment of overall disease activity on a 21-numbered circle visual analogue scale (VAS) (0 = no disease activity; 10 = maximum disease activity; 2) parent's or child's assessment of pain on a 21-numbered circle VAS (0 = no pain; 10 = maximum pain); 3) parent's or child's assessment of the activity of joint disease; 4) morning stiffness duration, scored on a 10-point scale as follows: absent (score = 0); less than 15 minutes (score = 2); 15-30 minutes (score 4); 30 minutes-1 hour (score = 6); 1-2 hours (score = 8); > 2 hours (score =10). We provided evidence of the validity and reliability of these four PCROs, showing that

they could be appropriate instruments to remotely monitor the disease activity of JIA, as reported in chapter 4.

On the other hand, we showed that the parent/patient global assessment of wellbeing might be an imperfect indicator of disease activity in patients with JIA, because it can be affected by several other factor irrespective of disease activity, such as persistent pain, functional ability, treatment burden, medications' side effects and psychosocial aspects (chapter 3). Therefore, we decided to rule out this PCRO as a component of the new PCROs-based score for JIA activity.

Finally, in chapter 5, we proposed the parent/child Juvenile Arthritis Disease Activity Score (par/childJADAS) as a new disease activity tool for JIA, solely based on PCROs. The parJADAS and childJADAS are calculated as the simple linear sum of the scores of their 4 components, which are the 4 above-mentioned PCROs. The parJADAS and the childJADAS exhibited very good measurement properties, possessing good construct validity, discriminant and predictive ability, internal consistency, and responsiveness to change. A regular home-completion of parJADAS and the childJADAS through electronic devices could be used for the remote assessment of the disease activity and telehealth, leading to an improvement of the quality of care of patients with JIA.

Chapter 7

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Chapter 8

Curriculum vitae

Main Research Fields

1) Clinical outcome measures and treatment strategies in juvenile idiopathic arthritis
2) Clinical characterization of autoinflammatory diseases
3) Identification of clinical and biological risk factors for the co-occurrence of autoimmune diseases in patients with chronic rheumatic disease

Research fellowship (years 2019-2022)

1) 01/06/2021-31/05/2022: Clinical and research fellowship at IRCCS Istituto Giannina Gaslini, Clinica Pediatrica e Reumatologia, EULAR Centre of Excellence in Rheumatology 2008-2023: clinical and research activity as part of the "Comparison of STep-up and step-down therapeutic strategies in childhood ARthritiS" (STARS)" trial.

List of publications (years 2019-2022)

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14) **Naddei R,** Orlando F, Aloj G, De Matteis A, Alessio M, Differential diagnosis of hypoalbuminemia in childhood: Protein Losing Enteropathy associated to Systemic Lupus Erythematosus in a young boy, Eur J Gastroenterol Hepatol. 2020 Jan;32(1):127-129. doi: 10.1097/MEG.0000000000001480.

Participation in clinical trials according to ICH GCP

1) 20/02/2020 – Current: CAIN457F2304/E1: An extension study of subcutaneous Secukinumab to evaluate the long-term efficacy, safety and tolerability up to 4 years in patients with Juvenile Idiopathic Arthritis subtypes of Juvenile Psoriatic Arthritis and ERA (Participation as sub-investigator)
2) 12/02/2020 – Current: I4V-MC-JAHX: A Phase 3 multicenter study to evaluate the long-term safety and efficacy of baricitinib in patients from 1 year to less than 18 years of age with Juvenile Idiopathic Arthritis (JIA) (Participation as Joint Assessor)
3) 16/10/2019 – Current: I4V-MC-JAHV: A randomized, double-blind, placebo-controlled, withdrawal, safety and efficacy study of oral Baricitinib in patients from 2 years to less than 18 years old with Juvenile Idiopathic Arthritis (JIA) (Participation as Joint Assessor)

Abstracts and Communications (years 2019-2022)

1. **Naddei R**, Bovis F, Ridella F, Trincianti C, Pastore S, Minden K, Ekelund M, Barone P, Scala S, Patrone E, Ruperto N, Ravelli A, Consolaro A. The parent/child juvenile idiopathic arthritis disease activity score: responsiveness to change and factor analysis. Proceedings of the 28th European Paediatric Rheumatology Congress (PReS 2022), Pediatric Rheumatology 2022, 20(Suppl 2):75. *(poster selected for the guided poster tour on Juvenile Idiopathic Arthritis at the main Congress and at the Young Investigator Meeting*)
2. Burrone M, Guazzi M, **Naddei R**, Spelta M, Malattia C, Disma NM, Ravelli A, Consolaro A, Oral midazolam before intra-articular corticosteroid injections in juvenile idiopathic arthritis, Proceedings of the 28th European Paediatric Rheumatology Congress (PReS 2022), Pediatric Rheumatology 2022, 20(Suppl 2):75.
3. Dellepiane M, Pescio E, Spelta M, **Naddei R**, Burrone M, Trincianti C, Ridella F, Cuttica R, Estmann A, Kamphuis A, Ravelli A, Ruperto R, Consolaro R, Impact of medications' side effects on JIA patients' health related quality of life and well-being, Proceedings of the 28th European Paediatric Rheumatology Congress (PReS 2022), Pediatric Rheumatology 2022, 20(Suppl 2):75.
4. **Naddei R**, Amico M, Castaldo M, Alessio M. Frequency and clinical features of SARS-CoV-2 infection in a cohort of patients with juvenile idiopathic arthritis. 27th European Paediatric Rheumatology Congress (PReS 2021) Virtual. 19-21 September 2021, Pediatric Rheumatology 2021, 19(Suppl 1):155
5. Traverso C, **Naddei R**, Lastella T, Aversano F, Alessio M. Psychological symptoms during COVID-19 pandemic in a cohort of patients with juvenile idiopathic arthritis, 27th European Paediatric Rheumatology Congress (PReS

2021) Virtual. 19-21 September 2021, Pediatric Rheumatology 2021, 19(Suppl 1):155

6. F. Orlando, M. Tardi, D. De Brasi, **R. Naddei,** R. Borrelli, M. Alessio, L. Martemucci, Expanding the autoinflammatory phenotype of sideroblastic anemia with immunodeficiency, fevers and development delay (SIFD) syndrome, 19-21 September 2021, Pediatric Rheumatology 2021, 19(Suppl 1):155
7. F. Ridella, C. Trincianti, M. Spelta, **R. Naddei**, C. N. Herrera, C. Malagon, O. Arguentes, A. Ibanez Estrella, A. Kondi, N. Ruperto, A. Ravelli, A. Consolaro, What does the patient well-being VAS tell us when the physician global assessment score is zero? Analysis of a large multinational dataset, 19-21 September 2021, Pediatric Rheumatology 2021, 19(Suppl 1):155
8. **Naddei R**, Di Gennaro S, Troncone R, Alessio M, Discepolo V. A family history of autoimmunity is a risk factor for celiac disease and juvenile idiopathic arthritis co-occurrence. 6th World Congress of PGHAN, 02-05 June 2021. Abstracts, Journal of Pediatric Gastroenterology and Nutrition: May 2021 - Volume 72 - Issue - p 1-1313
9. **Naddei R,** Di Gennaro S, Troncone R, Alessio M, Discepolo V., A family history of autoimmunity is a risk factor for celiac disease and juvenile idiopathic arthritis co-occurrence, 28th United European Gastroenterology Week Virtual 2020, United European Gastroenterology Journal 2020, Vol. 8(8S) *(selected for oral communication at the common interest group meeting of the European Society for Study of Coeliac Disease)*
10. Mozzillo F, Orlando F, **Naddei R**, Alfani R, Tommasini A, Alessio M, Systemic autoinflammatory disease resembling very early onset inflammatory bowel

disease: a familial case report, 26th European Paediatric Rheumatology Congress (PReS 2020), 23-25 September 2020, Pediatric Rheumatology Vol 18 Suppl. 2.

11. Porfito C, **Naddei R**, Orlando F, Amico M, Mozzillo F, Lastella T, Catzola A, Alessio M, The diagnostic challenge of PAMI syndrome: a case report, 26th European Paediatric Rheumatology Congress (PReS 2020), 23-25 September 2020, Pediatric Rheumatology Vol 18 Suppl. 2.
12. Orlando F, **Naddei R**, Ranucci G, Tardi M, Mauro A, Catzola A, Borrelli R, Martemucci L, Sottile R, Alessio M, Kawasaki disease during COVID-19 epidemic, 26th European Paediatric Rheumatology Congress (PReS 2020), 23-25 September 2020, Pediatric Rheumatology Vol 18 Suppl. 2.
13. **Naddei R**, Di Gennaro S, Troncone R, Discepolo V, Alessio M, A family history of autoimmunity is a risk factor for celiac disease and juvenile idiopathic arthritis co-occurrence, 26th European Paediatric Rheumatology Congress (PReS 2020), 23-25 September 2020, Pediatric Rheumatology Vol 18 Suppl. 2.
14. Alfani R, **Naddei R,** Vincenzi A, Viscogliosi F, Paonessa A, Catzola A, Alessio M, Vaccination coverage in a cohort of patients with juvenile idiopathic arthritis: a single-centre experience, 26th European Paediatric Rheumatology Congress (PReS 2020), 23-25 September 2020, Pediatric Rheumatology Vol 18 Suppl. 2.
15. **Naddei R**, Esposito C, Orlando F, Alfani R, Discepolo V, Alessio M, Screening for antithyroid antibodies in children with juvenile idiopathic arthritis: a single-centre experience from Southern Italy, 26th European Paediatric Rheumatology Congress (PReS 2020), 23-25 September 2020, Pediatric Rheumatology Vol 18 Suppl. 2.
16. Lastella T, **Naddei R**, Orlando F, Porfito C, Mozzillo F, Amico M, Alessio M, The muscoloskeletal manifestations of scurvy: a diagnostic challenge for the

rheumatologist, 26th European Paediatric Rheumatology Congress (PReS 2020), 23-25 September 2020, Pediatric Rheumatology Vol 18 Suppl. 2.

17. Amico M, **Naddei R,** Pierri L, Alfani R, Lastella T, Porfito C, Alessio M, Scleroderma-polymyositis overlap syndrome in pediatric age: a case report, 26th European Paediatric Rheumatology Congress (PReS 2020), 23-25 September 2020, Pediatric Rheumatology Vol 18 Suppl. 2.
18. I. Avrusin, **R. Naddei**, F. Ridella, G. Januskeviciute, M. Kostik, B. Whitehead, R. Gallizzi, E. Smolewska, S. Pastore, P. Hashkes, J. F. Swart, N. Ruperto, A. Ravelli, A. Consolaro, Development of the parent version of the juvenile arthritis disease activity score cut-offs for moderate and high disease activity states in juvenile idiopathic arthritis in a large multinational patient sample, EULAR Congress 2020, Annals of the Rheumatic Diseases Jun 2020, 79 (Suppl 1) 1781

Invited as a speaker or moderator (years 2019-2022)

- Course "Una tempesta di infiammazione", Napoli, 18/06/2022.
- Course "Progetto sul monitoraggio delle reazioni avverse successive all'uso combinato dei diversi farmaci in soggetti affetti da artrite reumatoide infantile", Napoli, 12/11/2021.
- Congress "Gastroenterologia Pediatrica a Napoli 2021: quinto incontro", Napoli, 26-27/01/2021.
- Common interest group meeting of the European Society for Study of Coeliac Disease (ESsCD), online, 11/10/2020.

Role in Scientific Societies

- Member of the Paediatric Rheumatology European Association

- Member of the International Society of Systemic Auto-Inflammatory Diseases
- Member of the Italian Society of Pediatric Rheumatology
- Member of the Italian Society of Pediatrics
- Reviewer for the international scientific medical journal "Pediatric Rheumatology Online Journal"

Teaching Activities

- 05/04/2022: Professor of a small group teaching activity of the Course of Pediatrics of the University of Genoa, held online, with a lecture on the differential diagnosis of arthritis in childhood.
- 13/05/2021: Professor of the Course in Pediatric Rheumatology at the Residency School of Pediatrics of the University of Naples Federico II, held online, with a lecture entitled: "Inquadramento dell'artrite in età pediatrica".
- 15/03/2021-16/09/2021: Tutor of the blended CME Course "Oltre la febbre: La telemedicina nella gestione del paziente con febbre mediterranea familiare".