RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Drivers of non-zero physician global scores during periods of inactive disease in juvenile idiopathic arthritis

Alessandra Alongi,[1] Gabriella Giancane,[2] Roberta Naddei,[2,3] Valentina Natoli,[4] Francesca Ridella,[4] Marco Burrone,[5] Silvia Rosina,[2] Gaelle Chedeville,[6] Ekaterina Alexeeva,[7] Gerd Horneff,[8] Ivan Foeldvari,[9] Giovanni Filocamo,[10] Tamàs Constantin,[11] Nicolino Ruperto ![ORCID] ,[12] Angelo Ravelli ![ORCID] ,[4,13] Alessandro Consolaro,[4,14] for the Pediatric Rheumatology International Trials Organization (PRINTO)

ABSTRACT

Objective To investigate the frequency in which the physician provides a global assessment of disease activity (PhGA) >0 and an active joint count (AJC)=0 in children with juvenile idiopathic arthritis (JIA) and search for determinants of divergence between the two measures.

Methods Data were extracted from a multinational cross-sectional dataset of 9966 patients who had JIA by International League of Associations for Rheumatology criteria, were recruited between 2011 and 2016, and had both PhGA and AJC recorded by the caring paediatric rheumatologist at the study visit. Determinants of discordance between PhGA>0 and AJC=0 were searched for by multivariable logistic regression and dominance analyses.

Results The PhGA was scored >0 in 1647 (32.3%) of 5103 patients who had an AJC of 0. Independent associations with discordant assessment were identified for tender or restricted joint count >0, history of enthesitis, presence of active uveitis or systemic features, enthesitis-related or systemic arthritis, increased acute phase reactants, pain visual analogue scale (VAS)>0, and impaired physical or psychosocial well-being. In dominance analysis, tender joint count accounted for 35.43% of PhGA variance, followed by pain VAS>0 (17.72%), restricted joint count >0 (16.14%) and physical health score >0 (11.42%).

Conclusion We found that many paediatric rheumatologists did not mark a score of 0 for patients who they found not to have active joints. The presence of pain in joints not meeting the definition of active joint used in JIA was the main determinant of this phenomenon.

Key messages

What is already known about this subject?
► The physician global assessment of disease activity (PhGA) is a key outcome measure of juvenile idiopathic arthritis (JIA).
► Several studies have shown that many clinicians do not mark the PhGA as 0 for patients who have apparent resolution of active disease.

What does this study add?
► This study investigated the frequency of disparity between a PhGA>0 and the absence of active joints and sought for determinants of discordance between the two measures.
► The PhGA was scored >0 in a sizeable percentage (32.3%) of 5103 patients who were found to have no active joints.
► The presence of joint pain was the main determinant of the divergence between a PhGA>0 and an active joint count of 0.

How might this impact on clinical practice or further developments?
► This study should prompt the revision of current criteria for inactive disease in JIA to require the absence of physician-reported joint pain related to JIA activity.
► The study findings highlight the need for international consensus efforts aimed at developing practical guidance for PhGA scoring in JIA.

INTRODUCTION

The physician's global assessment of disease activity (PhGA) is a key outcome measure of juvenile idiopathic arthritis (JIA). It consists of the rating of the overall level of child's disease activity on a 10 cm or 21-numbered circle visual analogue scale (VAS), with anchors of '0=no activity' and '10=maximum activity'. The PhGA is a complex construct that captures the examiner's subjective appraisal of patient's disease activity at the time of the visit and integrates the information obtained from clinical history with the findings of clinical assessment.

The PhGA has been found to possess strong responsiveness to clinically important

change[1 2] and to be a valid and reliable indicator of the overall JIA activity in all stages of the illness.[3] Furthermore, it has served as the gold standard against which other newly developed descriptors of the patient's condition or state were compared with establish their criterion (concurrent) and construct validity.[4–7] Based on its good measurement properties, the PhGA has been incorporated in the main composite endpoints for JIA, including the core set of variables of the American College of Rheumatology (ACR) Pediatric 30 response criteria,[8] the preliminary criteria for clinical remission in JIA,[9] the ACR provisional criteria for defining clinical inactive disease (ID) in JIA,[4] and the various versions of the Juvenile Arthritis Disease Activity Score (JADAS).[10–12]

The ACR provisional criteria for defining clinical ID in JIA, published in 2011[4] (thereafter called '2011 ID criteria'), are currently the most popular method to establish the state of complete disease quiescence in JIA. By these criteria, a patient is classified as being in ID when all these conditions are met: (1) absence of active joints; (2) absence of systemic manifestations attributable to JIA; (3) absence of active uveitis; (4) normal acute phase reactants; (5) a PhGA indicating no disease activity (ie, placed at the lowest end of the scale used) and (6) morning stiffness lasting ≤15 min.

By the fifth criterion, the 2011 ID definition requires that the PhGA is marked as 0 on the VAS to enable the classification of the patient's status as ID. However, some investigators have noticed the tendency of some clinicians not to mark their VAS for global assessment at exactly 0, even on resolution of active disease (ie, when all the other ID criteria are met).[7 13 14] This drawback has led to modify the ID criteria in some recent therapeutic studies by setting the minimum score of the PhGA at 1[15–17] or even at 2.[18] Notably, this phenomenon was seen with the use of the 21-circle VAS,[19] which is thought to avoid the aversion to extremes often seen on the horizontal line VAS,[20] indicating that it does not depend on the type of VAS used.

Thus far, the reasons that explain why the PhGA VAS is not scored as 0 in patients who would otherwise be classified as being in ID by the remaining criteria have seldom been investigated. Because the PhGA is mostly driven by joint symptoms, and the PhGA and the count of active joints are the two main physician-centred measures included in ID criteria, the analysis of their discordance may be of foremost importance to address the issue. Clarifying this inconsistency is important as the use of ID criteria in the assessment of the effectiveness of the modern therapeutic agents and in the implementation of the treat-to-target strategy[21] make it essential that the PhGA is scored accurately.

To gain insights from the real world of clinical practice, we evaluated in a large multinational dataset of JIA patients the percentage of instances in which the physician provided a PhGA>0 despite the absence of joints with active arthritis and sought for the determinants of divergence between the two measures.

METHODS

Study design and patient selection

Data were extracted from three cross-sectional datasets of patients meeting the International League of Associations for Rheumatology (ILAR) criteria for JIA[22]. The first included 9081 patients recruited between April 2011 and November 2016 in a worldwide survey of the epidemiology, treatment and outcome of JIA (EPOCA study).[23] ;the other two datasets were stored at the study center and included 1091 patients.

The characteristics of these patients have been reported elsewhere.[14 23] For the present analysis, we selected 9966 patients for whom both PhGA and active joint count (AJC) recorded at the time of clinical assessment were available.

Outcome measures

The PhGA was rated on a 21-numbered circle VAS, ranging from 0 (=no activity) to 10 (=maximum activity). The assessment of joint disease was made by the caring physician, who recorded for each of the 73 joints included in the standard articular examination the presence of swelling, tenderness/pain on motion and limited range of motion, as reported.[24] A joint was defined as active if it displayed swelling or, in case swelling was absent or not detectable (as in the case of cervical spine or hip), pain/tenderness plus restricted motion. The remaining components of the 2011 ID criteria (active systemic manifestations, active uveitis, elevated acute phase reactants and morning stiffness) were defined as per the original study.[4]

Based on their topographic location and size, joints were divided into proximal (cervical spine, temporomandibular, shoulder, hip, sacroiliac), distal large (elbow, wrist, knee, tibio-tarsal, sub-talar and intertarsal) and distal small (hand metacarpophalangeal and proximal and distal interphalangeal and foot metatarsophalangeal and interphalangeal). Articular and extra-articular damage was assessed through the Juvenile Arthritis Damage Index (JADI).[25] Laboratory tests included erythrocyte sedimentation rate (ESR) and C reactive protein (CRP).

Before the physician assessment, a parent or guardian completed a parent proxy-report version of a multidimensional questionnaire, translated into each national language. The questionnaire includes assessments of the child's physical function, overall well-being, pain, health-related quality of life, morning stiffness, disease status (remission, continued activity or disease flare), and satisfaction with illness outcome.[26]

The presence of ID was also assessed through the JADAS10, a composite disease activity score that incorporates the following four variables: PhGA, parent assessment of child's well-being, AJC, and ESR or CRP. The first two items are scored on a 0–10 scale, the AJC totals the number of active joints up to a number of 10 joints, and the ESR or CRP are transformed from mm/hour or mg/dL, respectively, to a 0–10 scale; the total score ranges

from 0 to 40. The presence of ID is defined when the JADAS10 score is ≤1.[27]

Statistical analysis

Descriptive statistics were used to summarise patients' characteristics. Bivariate comparisons were performed by means of Mann-Whitney U test for continuous variables and Pearson's χ^2 test or Fisher test for categorical variables.

To evaluate the effect of candidate variables on the probability of a PhGA>0, a set of binomial generalised linear (logistic) regression models was estimated. Numeric predictors were dichotomised 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)[28] and Tiur's R_2,[29] and by computing the area under the receiver operating curve (AUC-ROC) with 10-fold cross-validation repeated 10 times.

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.[30] The McFadden R_2 statistic was used to calculate general dominance weights. We further obtained bootstrap general dominance values, including estimated bootstrap values of general dominance for each variable and their corresponding SEs using McFadden's measure as a fit index and 1000 permutations.

Multivariable analyses were performed on patients with complete data for all study variables. However, to examine the impact of missing data, we performed a multiple imputation analysis under missing at random assumption by means of chained equations with 50 multiple imputation datasets using the MICE package available in R.

All analyses were conducted using the R Statistical language (V.4.0.3; R Core Team, 2020) on Windows 10×64 (build 19042) and, for dominance analysis, using the package dominance analysis (V.2.0.0; Claudio Bustos Navarrete and Filipa Coutinho Soares, 2020).

RESULTS
Analysis of discordance between PhGA, AJC and other ID criteria

Among the 9966 patients with the main outcome data (ie, PhGA and AJC) available, we identified 5103 patients with an AJC of 0. Within this subgroup, the PhGA was scored >0 in 1647 (32.3%) patients. Of these patients, 532 (32.3%) had a score of 0.5, 488 (29.6%) of 1, 141 (8.5%) of 1.5, 189 (11.4%) of 2 and 297 (18.0%) of >2. Among the 7265 patients with complete data available for all study variables, 3491 had an AJC of 0.

We, then, investigated the impact of not meeting each individual item of the 2011 ID criteria in patients who had an AJC of 0 by drawing an UpSet plot, where distinct combinations of items were ranked by frequency (figure 1). In 536 (14.6%) patients, the PhGA was the sole non-met criterion, which made it the single most frequent reason for not meeting the 2011 ID definition in patients with no active joints. Patients with non-zero PhGA scores who met all other ID criteria had a median PhGA value of 1 (IQR 0.5–1.5).

Comparison of clinical features and outcome measures between patients with discordance between PhGA and AJC

Table 1 shows the comparison of demographic and clinical features and physician-reported and parent-reported outcomes between patients with no active joints who had the PhGA scored as 0 or >0. Compared with patients with concordant evaluations (ie, with both AJC and PhGA scores as 0), those with divergence between the two assessments (ie, with an AJC=0 and a PhGA>0)
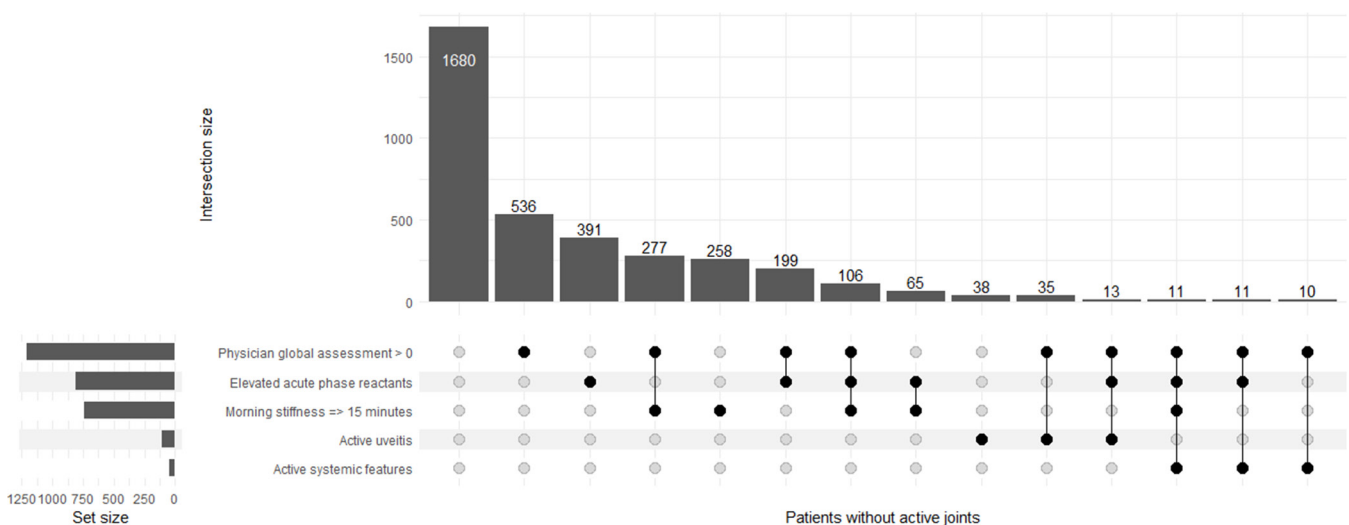

Figure 1 UpSet plot showing distinct combinations of items of 2011 inactive disease criteria ranked by frequency in patients with no active joints.

Table 1 Comparison clinical features and outcome measures between JIA patients with no active joints who had the PhGA scored as 0 or >0

	Patients with PhGA=0 (n=3456)	Patients with PhGA>0 (n=1647)	P value
Female	1194 (35) (0)	551 (33) (0)	0.4
Mean (SD) age at disease onset, years	5.7 (4.0) (0.1)	6.9 (4.4) (0.1)	<0.001
Mean (SD) age at visit, years	11.0 (4.5) (0)	11.7 (4.5) (0)	<0.001
Mean (SD) disease duration, years	5.3 (3.7) (0)	4.8 (3.8) (0)	<0.001
ILAR category	(0)	(0)	<0.001
Systemic arthritis	417 (12)	207 (13)	
Oligoarthritis	1654 (48)	590 (36)	
RF-negative polyarthritis	729 (21)	383 (23)	
RF-positive polyarthritis	79 (2.3)	81 (4.9)	
Psoriatic arthritis	110 (3.2)	62 (3.8)	
ERA	298 (8.6)	224 (14)	
Undifferentiated arthritis	169 (4.9)	100 (6.1)	
Enthesitis by history	18 (0.5) (2.1)	99 (6.2) (2.7)	<0.001
Dactylitis by history	22 (0.6) (2.1)	18 (1.1) (2.4)	0.082
Psoriasis by history	10 (0.3) (0)	8 (0.5) (0)	0.3
Other items of 2011 ID criteria			
Elevated acute phase reactants*	387 (14) (21.7)	309 (23) (18.2)	<0.001
Active systemic features*	11 (0.3) (0.9)	44 (2.7) (1.3)	<0.001
Active uveitis*	76 (2.3) (2.5)	74 (4.6) (2.7)	<0.001
Morning stiffness ≥15 min*	492 (14) (0.7)	559 (34) (0.9)	<0.001
Physician-reported outcomes			
Tender joint count >0	54 (1.6) (0)	396 (25) (0)	<0.001
Restricted joint count >0	465 (13) (0)	550 (33) (0)	<0.001
Proximal tender joints count >0	18 (0.5) (0)	146 (8.9) (0)	<0.001
Distal large tender joints count >0	38 (1.1) (0)	289 (18) (0)	<0.001
Distal small tender joints count >0	5 (0.1) (0)	70 (4.3) (0)	<0.001
JADI-articular >0	286 (8.4) (1.3)	292 (18) (1.6)	<0.001
JADI-extra-articular >0	229 (6.6) (1.3)	141 (8.5) (1.6)	0.028
Parent-reported outcomes			
Well-being VAS >0	1238 (36) (0.6)	1110 (68) (1.2)	<0.001
Disease activity VAS >0	1092 (32) (1.7)	1131 (70) (1.9)	<0.001
Pain VAS >0	1054 (31) (0.6)	1101 (67) (0.7)	<0.001
Physical function score >0	1034 (30) (1.3)	904 (55) (1.8)	<0.001
Physical health score >0	1484 (44) (1.3)	1205 (75) (1.8)	<0.001
Psychosocial health score	1560 (46) (2.1)	1061 (66) (2.9)	<0.001
Satisfied with illness outcome	3114 (91) (0.8)	1189 (73) (1.6)	<0.001
Inactive disease by the JADAS10	1956 (76) (25.8)	297 (23) (22.4)	<0.001

Data are the number (percentage) unless otherwise indicated. The percentage of missing data is indicated in the latter parentheses.
*Defined as in 2011 ID criteria.
ERA, Enthesitis-related arthritis; ID, inactive disease; JADAS, Juvenile Arthritis Disease Activity Score; JADI, Juvenile Arthritis Damage Index; JIA, juvenile idiopathic arthritis; PhGA, physician global assessment of overall disease activity; RF, rheumatoid factor; VAS, visual analogue scale.

Variable		N	Odds ratio		p
Elevated acute phase reactants		3491	■	1.64 (1.34, 1.99)	<0.001
Active systemic features		3491	■	3.97 (1.85, 8.98)	<0.001
Active uveitis		3491	■	4.65 (2.98, 7.25)	<0.001
Pain VAS > 0		3491	■	2.23 (1.82, 2.75)	<0.001
Tender joint count > 0		3491	■	19.45 (13.34, 29.22)	<0.001
Restricted joint count > 0		3491	■	4.04 (3.33, 4.91)	<0.001
Enthesitis (history)		3491	■	7.06 (3.67, 14.40)	<0.001
ILAR category	Oligoarthritis	1469	■	Reference	
	Systemic	452	■	1.55 (1.17, 2.04)	0.002
	RF negative polyarthritis	801	■	1.14 (0.91, 1.42)	0.245
	RF positive polyarthritis	124	■	1.75 (1.12, 2.73)	0.014
	Psoriatic	113	■	1.41 (0.87, 2.25)	0.159
	ERA	371	■	1.63 (1.21, 2.18)	0.001
	Undifferentiated	161	■	1.17 (0.77, 1.76)	0.458
Physical health score > 0		3491	■	1.55 (1.24, 1.94)	<0.001
Psychosocial health score > 0		3491	■	1.24 (1.03, 1.50)	0.026

1 2   5 10 20

Figure 2 Forest plot based on the results of multivariable logistic regression analysis of the factors associated with discordance between the physician global assessment of disease activity and the active joint count. Complete data were available on 3491 patients. The area under the receiver operating curve of the model was 0.80. ERA, Enthesitis-related arthritis; ILAR, International League of Associations for Rheumatology; RF, rheumatoid factor; VAS, visual analogue scale.

had an older age at disease onset, were older and had a longer disease duration at the time of the study visit, and had more frequently rheumatoid factor (RF)-positive polyarthritis and enthesitis-related arthritis, history of enthesitis, ongoing active systemic features and uveitis, increased acute phase reactants, morning stiffness duration ≥15 min, one or more tender or restricted joints (either overall and in proximal and distal large and small joints), articular damage in at least one site, worse parent-reported outcomes, and a lower frequency of ID by the JADAS10. Notably, the latter finding was expected because the PhGA is one of the four components of the JADAS10.

Seventy-three per cent of the patients in the study sample had all outcome data available. The acute phase reactants (ESR and CRP) showed the highest frequency of missing data (21%).

Multivariable analysis of predictors of discordance between PhGA and AJC

For the multivariable analysis, complete data were available on 3491 patients. The best-fitting model obtained through logistic regression procedures, in which the divergence between AJC and PhGA (ie, PhGA=0 and AJC=0 vs PhGA>0 and AJC=0) was the dependent variable, is presented in figure 2. Independent associations with a discordant assessment were identified for tender or restricted joint count >0, history of enthesitis, presence of active uveitis or ongoing systemic features, an ILAR category of systemic arthritis, RF-positive polyarthritis and ERA, increased acute phase reactants, pain VAS>0 and impaired quality of live in the physical or psychosocial domains.

The findings yielded by multiple imputation analysis on the incomplete observations (were similar to those observed in the sample with all outcome data available,

with the exception of a significant association between RF-negative polyarthritis and PhGA (results not shown).

Dominance analysis

Next, we performed a dominance analysis to rank the relative contribution of predictive factors in explaining the variance in PhGA. This analysis confirmed that the tender joint count was the main determinant of the discordance between the PhGA and the AJC and accounted for 35.43% of the predicted variance, followed by pain VAS>0 (17.72%), restricted joint count >0 (16.14%), and physical health score >0 (11.42%) (figure 3). The model showed a substantial explanatory power (McFadden R_2=0.25, Tjur's R_2=0.31), although a sizeable proportion of the variance could not be explained.

Multivariable analysis of predictors of discordance between PhGA and other ID criteria

To gain further insights into the reasons that led the caring physician not to provide a score 0 on the PhGA on apparent resolution of active disease, we repeated univariable and multivariable analyses by comparing the 1680 patients who met all 2011 ID criteria, including a PhGA of 0, with the 536 patients who met all 2011 ID criteria, but had the PhGA scored as >0. These analyses revealed that a tender joint count >0 was the factor that led most frequently the physician to provide a score >0, followed by a restricted joint count >0, history of enthesitis, a pain VAS>0, an ILAR category of ERA or systemic arthritis and a physical health score >0 (table 2 and figure 4).

DISCUSSION

Our results confirm that many clinicians do not mark the VAS for PhGA at 0 on apparent resolution of active joint disease. In approximately one-third of our patients who were judged by the caring physician as having no
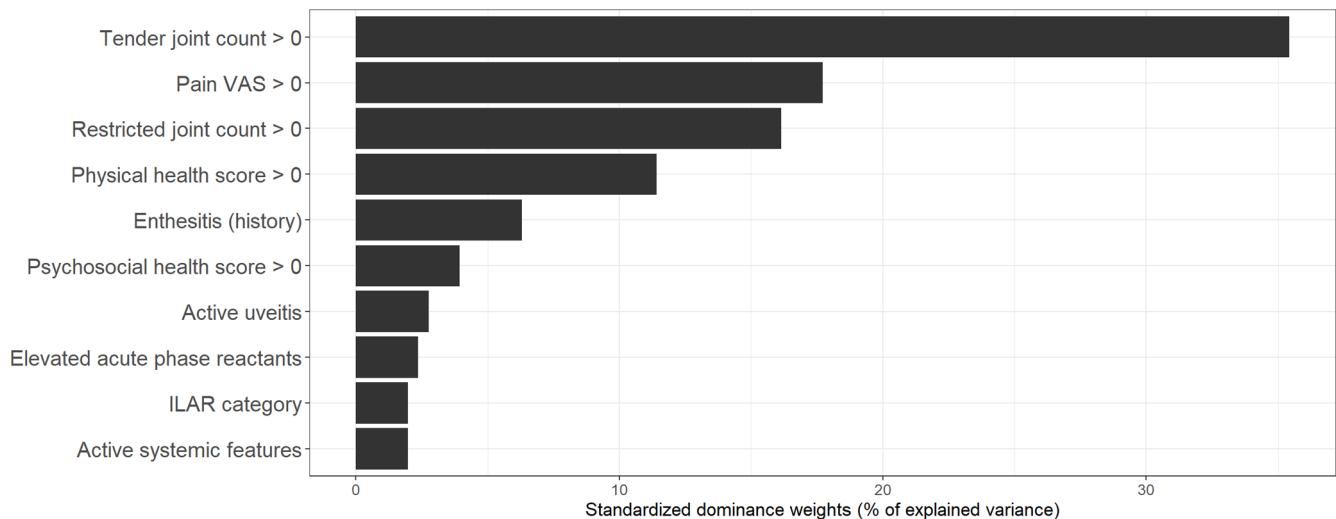
Figure 3 Dominance analysis of relative importance of predictive factors in explaining the variance in physician global assessment of disease activity. The average contribution of each covariate is standardised to be out of 100% (ie, divided by the sum of the general dominance weight of all variables, R_2=0.254) and reported as percentage of contribution to the predicted variance. ILAR, International League of Associations for Rheumatology; VAS, visual analogue scale.

active joints, the same physician provided a score >0 on the PhGA VAS. Furthermore, the PhGA was the sole non-met 2011 ID criterion in around 15% of these patients and was the single most frequent reason for not meeting the 2011 ID definition. In a sizeable proportion of cases (18%), the PhGA was scored as high as>2. This divergence is a matter of concern and has important implications for the use of the PhGA as an indicator of disease remission in clinical practice and therapeutic trials, especially when the application of the treat-to-target strategy is aimed for. Because the study patients were enrolled at 130 paediatric rheumatology centres in 49 countries, our results are likely generalisable to JIA patients seen worldwide and to physicians with varying degrees of training or experience, and practicing in diverse ethnic and cultural environments.

As expected, the lack of fulfilment of other 2011 ID criteria (ie, the presence of active systemic manifestations or uveitis and of increased acute phase reactants) accounted in part for the discordance between a PhGA>0 and the absence of active joints. It is noteworthy that in a number of patients the PhGA was scored as 0 in the presence of uveitis or systemic features. However, on multivariable analysis this phenomenon appeared to be explained by several other factors, the chief of which was the presence of joints with isolated tenderness/pain on motion (ie, of joints that displayed pain, but did not meet the definition of active joint used in JIA, which requires that joint pain is accompanied by swelling or limited range of motion). Other determinants included the presence of joints with isolated limited range of motion, a JIA category of systemic arthritis, RF-polyarthritis or ERA, a history of enthesitis, a VAS for parent-reported pain >0 and a decreased HRQL in the physical domain.

Our findings lead to raise some proposals aimed to increase the concordance between the PhGA and the other 2011 ID criteria. The marked impact of joint tenderness on the PhGA indicates that the presence of pain is highly valued by the physician in establishing ID. Thus, future revisions of ID criteria for JIA might consider the inclusion of physician-reported active disease related to joint pain.

The incorporation of the absence of parent/patient-reported pain among ID criteria is also worth of consideration, given the marked impact of pain on child's physical function and well-being. Guzman et al[31] found that most patients, parents and clinicians agreed on the upmost importance of pain and HRQL in describing the course of JIA, and suggested that the inclusion of these parameters could increase the relevance of ID definition for parents and patients. Notably, considerable concern has been raised by the observations of persistent pain in some children with JIA despite adequate treatment with biological medications and good disease control.[32–34] Needless to say that in the assessment of parent-reported and patient-reported pain particular attention should be paid to rule out pain unrelated to disease activity, such as mechanical pain secondary to structural joint damage or pain amplifications symptoms, which are frequent in paediatric rheumatic illnesses, especially in adolescent girl and in patients with long-standing disease.[35] However, to patients, remission means no pain, regardless of its cause. Thus, for the treatment of the overall disease across the multidisciplinary team and the understanding of the overall impact of disease, pain amplification and pain secondary to joint damage could be considered in remission criteria. Note that more than 30% of the patients scored by the physician as 0 on PhGA had parents' assessments indicating the presence of active disease and pain (see table 1).

The prominent role of enthesitis and ERA in influencing PhGA suggests that the absence of entheseal

Table 2 Comparison clinical features and outcome measures between JIA patients who had the PhGA scored as 0 or >0 and all other 2011 ID criteria met

	Patients with PhGA=0 (n=1680)	Patients with PhGA>0 (n=536)	P value
Female	1080 (64) (0.1)	343 (64) (0)	0.9
Mean (SD) age at disease onset, years	5.7 (4.0) (0)	6.9 (4.3) (0.2)	<0.001
Mean (SD) age at visit, years	11.0 (4.5) (0)	11.5 (4.6) (0)	0.008
Mean (SD) disease duration, years	5.2 (3.6) (0)	4.6 (3.6) (0)	<0.001
ILAR category	(0)	(0)	<0.001
Systemic arthritis	229 (14)	69 (13)	
Oligoarthritis	805 (48)	196 (37)	
RF-negative polyarthritis	362 (22)	121 (23)	
RF-positive polyarthritis	31 (1.8)	23 (4.3)	
Psoriatic arthritis	43 (2.6)	27 (5.0)	
ERA	145 (8.6)	72 (13)	
Undifferentiated arthritis	65 (3.9)	28 (5.2)	
Enthesitis by history	7 (0.4) (1.1)	22 (4.1) (0.2)	<0.001
Dactylitis by history	11 (0.7) (0.8)	7 (1.3) (0.2)	0.2
Psoriasis by history	3 (0.2) (0)	5 (1.0) (0)	0.023
Physician-reported outcomes			
Tender joint count >0	18 (1.1) (0)	101 (19) (0)	<0.001
Restricted joint count >0	226 (13) (0)	185 (35) (0)	<0.001
Proximal tender joints count >0	3 (0.2) (0)	33 (6.2) (0)	<0.001
Distal large tender joints count >0	16 (1.0) (0)	75 (14) (0)	<0.001
Distal small tender joints count >0	3 (0.2) (0)	12 (2.2) (0)	<0.001
JADI-articular >0	142 (8.5) (0.1)	96 (18) (0)	<0.001
JADI-extra-articular >0	147 (8.8) (0)	58 (11) (0)	0.15
Parent-reported outcomes			
Well-being VAS >0	453 (27) (0)	314 (59) (0)	<0.001
Disease activity VAS >0	367 (22) (1.7)	310 (59) (1.5)	<0.001
Pain VAS >0	358 (21) (0.4)	296 (55) (0.4)	<0.001
Physical function score >0	385 (23) (0)	217 (40) (0)	<0.001
Physical health score >0	592 (36) (1.0)	335 (64) (2.1)	<0.001
Psychosocial health score >0	680 (41) (1.7)	292 (56) (2.6)	<0.001
Satisfied with illness outcome	1565 (94) (0.5)	433 (82) (1.1)	<0.001
Inactive disease by the JADAS10	1467 (87) (0)	214 (40) (0)	<0.001

Data are the number (percentage) unless otherwise indicated. The percentage of missing data is indicated in the latter parentheses.
ERA, Enthesitis-related arthritis; JADAS, Juvenile Arthritis Disease Activity Score; JADI, Juvenile Arthritis Damage Index; JIA, juvenile idiopathic arthritis; PhGA, physician global assessment of overall disease activity; RF, rheumatoid factor; VAS, visual analogue scale.

inflammation should be added to the other extra-articular criteria in the 2011 ID definition. This modification, which was previously proposed by Shoop-Worrall and Hyrich,[36] would extend the validity of the criteria to the ERA/spondyloarthritis subset of JIA. Conversely, a history of dactylitis and psoriasis, which are features of juvenile psoriatic arthritis, did not affect the PhGA. However, the meaning of this observation is limited by the small number of patients with these features.

Taylor *et al*[20] found poor agreement among provider raters when scoring patients with JIA who had no clinically apparent disease activity. As in our study, the variable that influenced the PhGA most strongly in their analysis was joint pain. These investigators emphasised the inherent ambiguity and subjectivity of the PhGA, the implicit inexactitude of attempting to encapsulate a patient's overall condition by the use of any global score, and the challenges in the standardisation of scoring. However, discussion of the cases scenarios narrowed the disagreement, demonstrating that systematic training can improve the measurement characteristics of the PhGA. A wide variability between adult rheumatologists in rating their PhGA of patient with rheumatoid arthritis cases was seen, which led to highlight the need of consensus scores of

Variable		N	Odds ratio		p
Pain VAS > 0		2090		2.91 (2.21, 3.85)	<0.001
Tender joint count > 0		2090		19.87 (11.47, 36.44)	<0.001
Restricted joint count > 0		2090		4.04 (3.11, 5.23)	<0.001
Enthesitis (history)		2090		4.50 (1.60, 13.42)	0.005
ILAR category	Oligoarthritis	941		Reference	
	Systemic	279		1.63 (1.13, 2.34)	0.008
	RF negative polyarthritis	455		1.15 (0.84, 1.56)	0.379
	RF positive polyarthritis	51		1.85 (0.90, 3.70)	0.088
	Psoriatic	68		1.91 (1.02, 3.46)	0.037
	ERA	206		1.97 (1.33, 2.89)	<0.001
	Undifferentiated	90		1.17 (0.66, 2.03)	0.585
Physical health score > 0		2090		1.45 (1.10, 1.91)	0.007

1 2   5 10 20

Figure 4 Forest plot based on the results of multivariable logistic regression analysis of the factors associated with discordance between the physician global assessment of disease activity and all other 2011 inactive disease criteria. Complete data were available on 2090 patients. The area under the receiver operating curve of the model was 0.78. ERA, Enthesitis-related arthritis; ILAR, International League of Associations for Rheumatology; RF, rheumatoid factor; VAS, visual analogue scale; JIA, juvenile idiopathic arthritis.

physicians' global ratings.[37] In the field of inflammatory bowel disease, gastroenterologists have found it necessary to develop guidelines in an attempt to standardise the scoring of the PhGA.[38]

Our analysis is not without limitations. We could not investigate the relationship between the PhGA and novel biomarkers or imaging methods, especially ultrasound, which may establish disease remission more reliably than clinical assessment. The cross-sectional design of the study did not allow us to investigate the relationship between the observed discordance and disease outcomes, such as functional disability and radiographic progression. In addition, the potentially confounding effect of pain determinants external to disease activity, such as mechanical pain, fibromyalgia complaints, mood, anxiety, depression and patient and family coping could not be assessed. We should finally acknowledge that a substantial proportion of the variance in discordance between the PhGA and the NAJ could not be explained and that other items not captured in the study, such as intolerance of medication, could have made some physicians to provide a PhGA score >0.

In conclusion, our study confirms that many clinicians do not mark a score of 0 on the PhGA VAS, even for patients who they find not to have active joints or meet all the other 2011 ID criteria. The presence of joint pain was found to be the main determinant of this phenomenon. However, the observed variability between paediatric rheumatologists in rating the PhGA during periods of inactive disease highlights the need for international consensus efforts aimed at developing practical guidance for its scoring for patients with all categories of JIA.

Author affiliations
[1]Azienda Ospedaliera di Rilievo Nazionale e di Alta Specializzazione Civico Di Cristina Benfratelli, Palermo, Italy
[2]UOC Clinica Pediatrica e Reumatologia, Istituto Giannina Gaslini Istituto Pediatrico di Ricovero e Cura a Carattere Scientifico, Genova, Italy
[3]Department of Translational Medical Sciences, Pediatric Section, University of Naples Federico II, Napoli, Italy
[4]Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e Scienze Materno-Infantili, Università degli Studi di Genova, Genova, Italy
[5]Department of Pediatrics, Vittore Buzzi Children's Hospital, Università degli Studi di Milano, Milano, Italy
[6]Rheumatology Division, McGill University Health Center, Montreal Children's Hospital, Montreal, Quebec, Canada
[7]Children's Health of RAMS and IM Sechenov First Moscow State Medical University, Moscow, Russian Federation
[8]Pediatrics, Asklepios Clinic Sankt Augustin, Sankt Augustin, Germany
[9]Klinikum Eilbek, Hamburger Zentrum für Kinder- und Jugendrheumatologie, Hamburg, Germany
[10]UOC Pediatria Media Intesità di Cure, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy
[11]Unit of Paediatric Rheumatology, Semmelweis University, Budapest, Hungary
[12]Pediatria II - PRINTO, Istituto Giannina Gaslini Istituto Pediatrico di Ricovero e Cura a Carattere Scientifico, Genova, Italy
[13]Direzione Scientifica, Istituto Giannina Gaslini Istituto Pediatrico di Ricovero e Cura a Carattere Scientifico, Genova, Italy
[14]UOC Clinica Pediatrica e Reumatologia, Istituto Giannina Gaslini, Genova, Italy

involved in the EPOCA study. Participants gave informed consent to participate in the study before taking part.

ORCID iDs
Nicolino Ruperto http://orcid.org/0000-0001-8407-7782
Angelo Ravelli http://orcid.org/0000-0001-9658-0385

REFERENCES

1 Ruperto N, Ravelli A, Falcini F. Responsiveness of outcome measures in juvenile chronic arthritis. *Rheumatology* 1999;38:176–80.
2 Moretti C, Viola S, Pistorio A, *et al*. Relative responsiveness of condition specific and generic health status measures in juvenile idiopathic arthritis. *Ann Rheum Dis* 2005;64:257–61.
3 Palmisani E, Solari N, Magni-Manzoni S, *et al*. Correlation between juvenile idiopathic arthritis activity and damage measures in early, advanced, and longstanding disease. *Arthritis Rheum* 2006;55:843–9.
4 Wallace CA, Giannini EH, Huang B, *et al*. American College of rheumatology provisional criteria for defining clinical inactive disease in select categories of juvenile idiopathic arthritis. *Arthritis Care Res* 2011;63:929–36.
5 Ruperto N, Ravelli A, Murray KJ, *et al*. Preliminary core sets of measures for disease activity and damage assessment in juvenile systemic lupus erythematosus and juvenile dermatomyositis. *Rheumatology* 2003;42:1452–9.
6 Ruperto N, Pistorio A, Ravelli A, *et al*. The paediatric rheumatology international trials organisation provisional criteria for the evaluation of response to therapy in juvenile dermatomyositis. *Arthritis Care Res* 2010;62:1533–41.
7 Limenis E, Feldman BM, Achonu C, *et al*. Proposed core set of items for measuring disease activity in systemic juvenile idiopathic arthritis. *J Rheumatol* 2018;45:115–21.
8 Giannini EH, Ruperto N, Ravelli A, *et al*. Preliminary definition of improvement in juvenile arthritis. *Arthritis Rheum* 1997;40:1202–9.
9 Wallace CA, Ruperto N, Giannini E, *et al*. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. *J Rheumatol* 2004;31:2290–4.
10 Consolaro A, Ruperto N, Bazso A, *et al*. Development and validation of a composite disease activity score for juvenile arthritis. *Arthritis Rheum* 2009;61:658–66.
11 Consolaro A, Negro G, Chiara Gallo M, *et al*. Defining criteria for disease activity states in nonsystemic juvenile idiopathic arthritis based on a three-variable juvenile arthritis disease activity score. *Arthritis Care Res* 2014;66:1703–9.
12 Tibaldi J, Pistorio A, Aldera E, *et al*. Development and initial validation of a composite disease activity score for systemic juvenile idiopathic arthritis. *Rheumatology* 2020;59:3505–14.
13 Shoop-Worrall SJW, Verstappen SMM, Baildam E, *et al*. How common is clinically inactive disease in a prospective cohort of patients with juvenile idiopathic arthritis? The importance of definition. *Ann Rheum Dis* 2017;76:1381–8.
14 Giancane G, Campone C, Gicchino MF, *et al*. Determinants of discordance between criteria for inactive disease and low disease activity in juvenile idiopathic arthritis. *Arthritis Care Res* 2021;73:1722–9.
15 Guzman J, Henrey A, Loughin T, *et al*. Predicting which children with juvenile idiopathic arthritis will not attain early remission with conventional treatment: results from the ReACCh-Out cohort. *J Rheumatol* 2019;46:628–35.
16 De Benedetti F, Brunner HI, Ruperto N, *et al*. Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. *N Engl J Med* 2012;367:2385–95.
17 Otten MH, Prince FHM, Armbrust W, *et al*. Factors associated with treatment response to etanercept in juvenile idiopathic arthritis. *JAMA* 2011;306:2340–7.
18 Ruperto N, Lovell DJ, Quartier P, *et al*. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. *Lancet* 2008;372:383–91.
19 Filocamo G, Davì S, Pistorio A, *et al*. Evaluation of 21-numbered circle and 10-centimeter horizontal line visual analog scales for physician and parent subjective ratings in juvenile idiopathic arthritis. *J Rheumatol* 2010;37:1534–41.
20 Taylor J, Giannini EH, Lovell DJ, *et al*. Lack of concordance in interrater scoring of the provider's global assessment of children with juvenile idiopathic arthritis with low disease activity. *Arthritis Care Res* 2018;70:162–6.
21 Ravelli A, Consolaro A, Horneff G, *et al*. Treating juvenile idiopathic arthritis to target: recommendations of an international task force. *Ann Rheum Dis* 2018;77:819–28.
22 Petty RE, Southwood TR, Manners P, *et al*. International League of associations for rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol* 2004;31:390–2.
23 Consolaro A, Giancane G, Alongi A, *et al*. Phenotypic variability and disparities in treatment and outcomes of childhood arthritis throughout the world: an observational cohort study. *Lancet Child Adolesc Health* 2019;3:255–63.
24 Ravelli A, Viola S, Ruperto N, *et al*. Correlation between conventional disease activity measures in juvenile chronic arthritis. *Ann Rheum Dis* 1997;56:197–200.
25 Viola S, Felici E, Magni-Manzoni S, *et al*. Development and validation of a clinical index for assessment of long-term damage in juvenile idiopathic arthritis. *Arthritis Rheum* 2005;52:2092–102.
26 Bovis F, Consolaro A, Pistorio A, *et al*. Cross-cultural adaptation and psychometric evaluation of the juvenile arthritis multidimensional assessment report (JAMAR) in 54 languages across 52 countries: review of the general methodology. *Rheumatol Int* 2018;38:5–17.
27 Consolaro A, Bracciolini G, Ruperto N, *et al*. Remission, minimal disease activity, and acceptable symptom state in juvenile idiopathic arthritis: defining criteria based on the juvenile arthritis disease activity score. *Arthritis Rheum* 2012;64:2366–74.
28 McFadden D. Conditional logit analysis of qualitative choice behavior. *Frontiers in Econometrics* 1974;105–42.
29 Tjur T. Coefficients of determination in logistic regression models–a new proposal: the coefficient of discrimination. *Am Stat* 2009;63:366–72.
30 Azen R, Traxel N. Using dominance analysis to determine predictor importance in logistic regression. *J Educ Behav Stat* 2009;34:319–47.
31 Guzman J, Gómez-Ramírez O, Jurencak R, *et al*. What matters most for patients, parents, and clinicians in the course of juvenile idiopathic arthritis? A qualitative study. *J Rheumatol* 2014;41:2260–9.
32 Lomholt JJ, Thastum M, Herlin T. Pain experience in children with juvenile idiopathic arthritis treated with anti-TNF agents compared to non-biologic standard treatment. *Pediatr Rheumatol Online J* 2013;11:21.
33 Consolaro A, Ravelli A. Paediatric rheumatology: Juvenile idiopathic arthritis--are biologic agents effective for pain? *Nat Rev Rheumatol* 2013;9:447–8.
34 Anink J, Prince FHM, Dijkstra M, *et al*. Long-term quality of life and functional outcome of patients with juvenile idiopathic arthritis in the biologic era: a longitudinal follow-up study in the Dutch arthritis and biologicals in children register. *Rheumatology* 2015;54:1964–9.
35 Santaniello S, Ravelli A. The controversial role of wellbeing assessment in juvenile idiopathic arthritis. *Lancet Rheumatol* 2021;3:e85–6.
36 Shoop-Worrall SJW, Hyrich KL. Predicting remission remains a challenge in patients with juvenile idiopathic arthritis. *J Rheumatol* 2019;46:552–4.
37 Turk M, Pope JE. Physician global assessments for disease activity in rheumatoid arthritis are all over the map! *RMD Open* 2018;4:e000578.
38 Improvecarenow. Definitions of physician global assessment, 2015. Available: https://d3n8a8pro7vhmx.cloudfront.net/improvecarenow/pages/283/attachments/original/1456525231/PGA_Clinical_Guidelines.pdf?1456525231