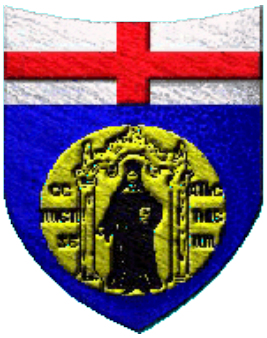

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Sviluppo e validazione di uno strumento composito di valutazione dell'attività di malattia nella dermatomiosite giovanile

Development and validation of a composite disease activity score for juvenile dermatomyositis

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Ai miei meravigliosi genitori e ai colleghi ed amici che mi hanno accompagnata e sostenuta lungo questo percorso

INTRODUCTION

Juvenile dermatomyositis (JDM) is a multisystem vasculopathic disease of presumably autoimmune etiology that primarily involves the skin and muscles, but may affect many other systems, namely the gastrointestinal tract, heart and lungs. It is also characterized by some peculiar and largely mysterious complications, such as lipodistrophy and calcinosis. Although the prognosis of JDM has markedly improved in the last three decades, there are still many patients who do not respond to first-line therapies and continue to have active disease. These patients are at risk of developing irreversible damage from the disease or its treatment. This damage may lead to permanent disability and affect the quality of life of patients and their families.

Evaluation of disease activity is a fundamental component of the clinical assessment of children with JDM, as persistently active disease plays a major role in causing disease-related damage and physical functional disability. Furthermore, measurement of the level of disease activity over time is important in assessing the effectiveness of therapeutic interventions in clinical trials and in monitoring the patient's course in daily care.

The optimal assessment of the level of disease activity in children with JDM requires the availability of standardized tools. Standardization is fundamental to ensure harmonization of assessments across different physicians and centers and facilitate the comparability of results of therapeutic trials and other research studies. Since JDM is a rare disease, research and clinical trials must involve

multicenter and international collaborations. Collaborative efforts of international experts are the best way to devise and validate standardized assessment tools and to foster their widespread use.

Many tools are currently available for the assessment of disease activity in JDM. However, most of the existing measures are lengthy, complex and fail to adequately distinguish disease activity from damage. Therefore, they remain essentially research tools and are rarely used in routine clinical practice. Another problem with most of these measures is that they address only a single disease domain and do not provide an overview of the overall disease impact. There remains, therefore, the need for a concise and easily administered score tool that is appropriate for use in clinical research, therapeutic trials, and routine care.

So far, no widely accepted definitions of JDM disease status (i.e. clinically inactive disease, minimal disease activity, moderate disease activity, high disease activity) are available. These definitions may represent useful treatment target states for both physicians and parents/patients and could be included as an outcome measure in future observational studies and clinical trials in JDM. A composite disease activity score, which is made up by pooling multiple individual measures of disease activity and provides a summary number on a continuous scale, is ideally suitable to measure the overall level of disease activity in a multisystem disease such as JDM and to establish the score thresholds (or cutoffs) that correspond to the various disease activity states.

The research project that is subject of this work is aimed at developing a composite disease activity score for JDM, named Juvenile DermatoMyositis

Activity Index (JDMAI), and at providing preliminary evidence of its validity.

In the first part of the work, the development and composition of the six preliminary versions of the JDMAI is described. In the second part, the new tool is preliminarily validated using three large multinational patient samples. In the final part of the project the validity of the JDMAI is prospectively tested in a sample of patients seen in daily practice.

FIRST PART: DEVELOPMENT OF THE JUVENILE DERMATOMYOSITIS ACTIVITY INDEX (JDMAI)

Introduction

Juvenile dermatomyositis (JDM) is a multisystem inflammatory disease of unknown etiology that primarily involves the skin and skeletal muscles, but may also affect visceral organs, particularly the gastrointestinal tract and lung [1,2]. Evaluation of disease activity is a fundamental component of the clinical assessment of children with JDM, as persistently active disease plays a major role in causing organ damage and functional disability.

In recent years, the treatment of JDM has been made more rational through the scrutiny of novel and traditional medications in randomized controlled trials [3, 4] and the publication of consensus-based expert advice on optimal management [5-10]. To substantiate these advances, there is the need for sensitive, precise, and feasible measures of disease activity.

A variety of instruments are available for measuring disease activity in JDM [11, 12], including global assessment scales, tools for quantification of muscle strength and skin manifestations, functional ability and quality of life questionnaires, muscle magnetic resonance imaging, electromyography, capillaroscopy, muscle histopathology, and serum muscle enzymes. However, due to the high variability in clinical presentation and course of JDM, no single measure

can reliably capture disease activity in all patients. Conversely, evaluation of all measures individually may raise methodological and statistical problems, especially when they are employed as end points in clinical trials.

To enhance standardization, core sets of variables for assessment of disease activity and therapeutic response in JDM have been established in parallel by the Pediatric Rheumatology International Trials Organization (PRINTO) [13] and the International Myositis Assessment and Clinical Studies Group (IMACS) [14-19]. However, these tools are primarily proposed for use in research and clinical trials, and are seldom applied in routine clinical care.

An alternative, pragmatic approach to the measurement of disease activity in JDM can be modeled on the so-called composite disease activity scores. These tools are made up by pooling individual measures of disease activity into a single instrument and aim to quantify the absolute level of activity by providing one summary number on a continuous scale. They are thought to enhance consistency in disease activity evaluation across physicians and may allow patients to better understand the meaning of disease activity by providing a single score number. Composite scores have been successfully introduced in juvenile idiopathic arthritis (JIA) [20-22].

At present, such measures do not exist for JDM. For this reason, the aim of the present study was to develop a composite disease activity score for JDM, called the Juvenile DermatoMyositis Activity Index (JDMAI), and to provide preliminary evidence of its validity.

Development of the JDMAI

The JDMAI was devised by a group of eight paediatric rheumatologists with 2 to > 30 years of experience in the assessment and care of children with JDM (S.R., A.C., P.V.D., G.C.V., K.N., C.P., N.R. and A.R.), who reached consensus on the individual measures to be included in the score. Investigators were asked to base their choice on their clinical experience and on a review of the pertinent literature. After extensive discussion on which items should be included in the tool, agreement among investigators was reached on the following four clinical domains: physician's global assessment of overall disease activity (PhGA) on a visual analogue scale (VAS) (where 0 = no activity and 10 = maximum activity); parent's/patient's global assessment of patient's overall wellbeing (PaGA) on a VAS (where 0 = best and 10 = worst); assessment of muscle strength; and assessment of skin disease activity.

Because no universally embraced scales for measurement of muscle strength and skin disease activity in JDM exist, it was decided to test various JDMAI versions that included different instruments for the assessment of these two constructs. For muscle strength, the selected tools were the Manual Muscle Testing 8 (MMT8) (score range 0 = worst to 80 = best) [23], the Childhood Myositis Assessment Scale (CMAS) (score range 0 = worst to 52 = best) [24, 25], and the hybrid MMT8/CMAS (hMC) (score range 0 = worst to 100 = best) [26]. To estimate the activity of skin disease, the physician's global assessment of the activity of skin disease on a 10-cm VAS (skin activity VAS, score range 0 = no activity to 10 = maximum activity) and the skin component of the Disease Activity Score (DAS)

(DAS skin, score range 0 = no activity to 9 = maximum activity) [27] were chosen.

In constructing the JDMAI, we realized that the score range of the three muscle strength tools was much wider than that of the other items. Furthermore, we noticed in the study patients that their scores were skewed towards the normal end of the scale. We therefore decided, in order to improve score distribution and avoid giving the muscle strength tools an excessive weight in the index, to express muscle scores in deciles. Decile calculation was performed by pooling the scores of all patients included in the study datasets (n = 627). Thus, the score range of all three muscle strength tools ranges from 0 to 10. For sake of consistency, scores were reversed to give them the same direction (i.e. 0 = best to 10 = worst) as the other JDMAI components. The minimum cutoffs (MMT8 < 22; CMAS < 6; hMC < 23) correspond to the maximum muscle score values of patients in the weakest decile (i.e. decile score = 10). The rule of score conversion in deciles is shown in **Table 1.** The six versions of the JDMAI tested in validation analyses and their theoretical range are presented in **Table 2**.

Table 1. Rule of conversion of the scores of muscle strength tools into decile scores.

MMT8	CMAS	hMC	Decile score
< 22	< 6	< 23	10
≥ 22 to < 33	≥ 6 to < 12	≥ 23 to < 34	9
≥ 33 to < 40	≥ 12 to < 19	≥ 34 to < 42	8
≥ 40 to < 48	≥ 19 to < 22	≥ 42 to < 50	7
≥ 48 to < 52	≥ 22 to < 28	≥ 50 to < 58	6

≥ 52 to < 58	≥ 28 to < 32	≥58 to < 64	5
≥ 58 to < 63	≥ 32 to < 37	≥ 64 to < 72	4
≥ 63 to < 70	≥ 37 to < 43	≥ 72 to < 81	3
≥ 70 to < 77	≥ 43 to < 48	≥ 81 to < 93	2
≥ 77 to < 80	≥ 48 to < 52	≥ 93 to < 100	1
80	52	100	0

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

JDMAI1	JDMAI2	JDMAI3	JDMAI4	JDMAI5	JDMAI6
Physician's global assessment of overall disease activity (0-10)					
Parent's/patient's global assessment of overall well-being (0-10)					
hMC in deciles (0-10)[a]		MMT8 in deciles (0-10)[a]		CMAS in deciles (0-10)[a]	
Skin VAS (0-10)	DAS skin (0-9)	Skin VAS (0-10)	DAS skin (0-9)	Skin VAS (0-10)	DAS skin (0-9)
Total score					
0-40	0-39	0-40	0-39	0-40	0-39

[a]See Table 1 for calculation of decile scores.

SECOND PART: PRELIMINARY VALIDATION OF THE JUVENILE DERMATOMYOSITIS ACTIVITY INDEX (JDMAI)

Study datasets

Three multinational samples composed of patients with probable or definite JDM by Bohan and Peter criteria [28, 29] were used to validate the JDMAI. The first was an inception cohort of 275 patients enrolled in a study aimed to validate prospectively the "Provisional PRINTO/American College of Rheumatology/European League Against Rheumatism Disease Activity Core Set for the Evaluation of Response to Therapy in Juvenile Dermatomyositis" [17]. All patients had active disease at study entry and were assessed at baseline and 6 months after a major therapeutic intervention. The second sample included 139 patients enrolled in a randomized controlled trial aimed to compare the efficacy and safety of prednisone alone with that of prednisone plus either methotrexate or ciclosporin [4]. The third sample comprised 213 patients followed in standard clinical care at 13 international pediatric rheumatology centers and evaluated prospectively at baseline and after a median of 5.9 months. For sake of brevity, the three datasets will hereafter be named PRINTO sample, JDM trial sample, and Routine sample, respectively. The proportion of patients who had definite JDM by the 2017 European League Against Rheumatism/American College of Rheumatology classification criteria [30] was 97.1% in the PRINTO sample and 98.6% in the JDM trial sample. These criteria could not be applied in the Routine sample due to the lack of sufficiently detailed information at disease onset for

most patients.

Clinical assessment in all patients comprised muscle strength measurement with MMT8, CMAS and hMC as well as quantification of the other aspects of disease impact through the traditional physician-centred or parent-reported outcome measures for JDM. These measures included, depending on the sample, the PhGA, PaGA, parent's assessment of the intensity of pain on a 10-cm VAS (0 = no pain; 10 = maximum pain), parent's assessment of fatigue on a 10-cm VAS (0 = no fatigue; 10 = maximum fatigue), calculation of overall disease activity through the total score of the DAS (DAS total, 0 = no activity; 20 = maximum activity) [27], assessment of muscle disease activity with the muscle component of the DAS (DAS muscle, 0 = no activity; 11 = maximum activity) [27] or physician's global assessment of muscle disease activity on a 10-cm VAS (muscle activity VAS, 0 = no activity; 10 = maximum activity) [31], and the assessment of physical function through the Childhood Health Assessment Questionnaire (CHAQ) (0 = best; 3 = worst) [32]. Health-related quality of life (HRQL) was assessed through the Child Health Questionnaire (CHQ), and expressed by the CHQ physical summary score (CHQ-PhS) and CHQ psychosocial summary score (CHQ-PsS) [33, 34]. Cumulative damage was assessed with the Myositis Damage Index (MDI) (0 = no damage; 35 = maximum damage) [31]. Laboratory tests included creatine kinase (CK).

Validation procedures

Validation of the JDMAI was conducted following the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) filter for outcome measures in rheumatology [35, 36]. Feasibility or practicality was determined by addressing the issues of brevity, simplicity and easy scoring [37]. Face and content validity were obtained as stated above.

Construct validity was assessed by calculating the correlations of the JDMAI with the outcome measures not included in the tool. Given that the JDMAI was devised to measure JDM disease activity and incorporates both muscle and skin components, it was predicted that its correlation with muscle activity VAS, DAS total, DAS muscle, MMT8, CMAS, hMC, skin activity VAS and DAS skin, which assess related constructs, would be moderate-to-high. Correlations with CK, pain VAS, fatigue VAS, CHAQ score, CHQ-PhS and CHQ-PsS were predicted to be moderate-to-low, as these measures combine the effect of disease activity with that of other constructs, including external factors unrelated to the disease. Correlations with MDI were predicted to be low as this tool measures a different construct. In JDM trial and Routine datasets, correlations were assessed at baseline visit. Correlations were computed using Spearman's rank statistics and were considered high if > 0.7, moderate if 0.4-0.7 and low if < 0.4 [38, 39].

Internal consistency was assessed using Cronbach's alpha coefficient [40] and was defined as follows: < 0.6 = poor, 0.6-0.64 = slight, 0.65-0.69 = fair, 0.7-0.79 = moderate, 0.8-0.89 = substantial, and > 0.9 = almost perfect [41]. The

internal structure of the JDMAI was examined using exploratory factor analysis [42], which can determine if a scale is measuring more than one construct. It generates factor loadings, which are measurements of how strongly the observed variables in the scale are associated with its latent factor(s).

To evaluate whether the JDMAI can differentiate between patients with varying levels of disease activity, we compared its scores between patients grouped using physicians' subjective estimation of current disease activity (rated as inactive disease or low, moderate or high disease activity), and parents' satisfaction with illness outcome. To evaluate satisfaction, parents were asked the question, 'Considering all the ways the illness affects your child, would you be satisfied if his/her condition remained stable/unchanged for the next few months?', which was to be answered yes or no [43]. It was expected that the JDMAI score was lower among patients judged by the physician as being in a state of inactive disease or whose parents were satisfied with illness outcome. Comparison among groups was made by the Mann-Whitney U test and the Kruskall-Wallis test, as appropriate.

Responsiveness of JDMAI to change between two consecutive visits was assessed by computing the standardized response mean (SRM), calculated as the mean change in score divided by the S.D. of individuals' change in score. According to Cohen [44], threshold levels for SRM were defined as follows: ≥ 0.2 = small, ≥ 0.5 = moderate, and ≥ 0.80 = good.

All statistical tests were two sided; a P value < 0.05 was considered statistically significant. The statistical packages used were 'Statistica' (release 6.1,

StatSoft, Tulsa, OK, USA), Stata release 9.2 (Stata Corporation, College Station, TX, USA), XLSTAT (version 1.02, Addinsoft, 2013), and R statistics (version 3.3.3) [The R foundation for Statistical Computing, Vienna, Austria (https://www.R-project.org/)].

Results

The main demographic and clinical features of the three patient datasets are shown in **Table 3**. The gender ratio and average age at disease onset were comparable across datasets, although patients in the Routine sample had a slightly younger disease presentation. On average, patients in all three datasets had short disease duration. As expected, patients in PRINTO and JDM trial samples, which comprised patients with active disease, had a higher level of disease activity than patients in the Routine sample, which included patients followed in routine clinical care. Patients who had health-related quality of life assessment available had a greater impairment in physical than in psychosocial well-being. The low MDI score reflects the average short disease duration of patients enrolled. The score values of the six versions of the JDMAI in the three patient samples are provided in **Table 4.**

Table 3. Demographic features and values of outcome measures of the three patient samples.

	Score Range	PRINTO sample N = 275	JDM trial sample N = 139	Routine sample N = 213
	Min – Max	Median (IQR)	Median (IQR)	Median (IQR)
Sex (Female)	-	168 (61.1%)	82 (59.0%)	132 (62.0%)
Age at disease onset	-	7.3 (4.2 - 10.2)	7.4 (4.5 - 10.6)	6.2 (4.0-9.1)
Age at 1st visit (years)	-	8.7 (5.9 - 12.7)	7.6 (4.7 - 10.8)	8.4 (5.0-12.3)
Disease duration (years)	-	0.6 (0.2 - 2.1)	0.2 (0.1 - 0.4)	0.5 (0.2-1.9)
PhGA	0-10	5.5 (3.4 - 7.2)	6.4 (5.0 – 8.0)	4.0 (1.0-7.0)
Muscle activity VAS	0-10	5.2 (2.9 – 7.4)	6.3 (5.0 – 8.0)	1.5 (0.0-4.0)
Skin activity VAS	0-10	5.0 (2.3 – 6.7)	5.0 (3.0 – 7.0)	2.0 (0.0-5.0)
DAS	0-20	12 (10-15)	13 (11 - 15)	6 (2-13)
DAS - muscle	0-11	6 (4 – 8)	7 (6 – 9)	2.5 (0-7)
DAS - skin	0-9	6 (5 – 7)	6 (5 – 7)	4 (1-7)
MMT8	0-80	48 (32 - 62)	46 (34-57)	74 (61-79)
CMAS	0-52	27 (13 - 36)	20 (13 - 33)	47.0 (34.0-52.0)
hMC	0-100	52 (35 - 71)	49 (34 - 63)	89.6 (68.1-97.6)
Creatine kinase, U/L	0 – 150*	251 (70-1395)	741 (155 – 2978)	103 (50- 688)
MDI	0-35	0.0 (0.0 – 4.0)	0.0 (0.0 – 1.1)	NA
PaGA	0-10	5.2 (3.0 – 7.4)	5.8 (4.4 - 7.0)	1.7 (0.0-5.0)
Pain VAS	0-10	3.2 (0.8 – 6.0)	5.0 (3.0 – 7.0)	1 (0.0-9.5)
Fatigue VAS	0-10	NA	NA	2 (0-8)
CHAQ	0-3	1.6 (1.0 – 2.5)	1.8 (1.3 - 2.5)	1.5 (1.0-2.2)

CHQ-PhS	40-60	32.0 (23.5 – 42.5)	15.6 (8.0 - 24.4)	NA
CHQ-PsS	40-60	45.9 (40.2 – 52.2)	40.0 (29.7 - 48.0)	NA.

IQR = Interquartile Range; NA = Not Available.

Table 4. Scores of the six versions of the JDMAI in the three patient samples.

	Score Range	PRINTO sample N=275	JDM trial sample N=139	Routine sample N=213
	Min – Max	Median (IQR)	Median (IQR)	Median (IQR)
JDMAI1	0-40	22 (15.9 - 27.1)	23.3 (19.3 - 27.9)	6.8 (1 - 17.5)
JDMAI2	0-39	22.2 (17.3 - 27.7)	25 (20.1 - 28)	8.3 (2 - 16)
JDMAI3	0-40	22.1 (15.9 - 27.4)	23.8 (19 - 28)	7.5 (1.5 - 17.5)
JDMAI4	0-39	22.2 (17.2 - 28.3)	24.1 (20.3 - 28)	8.8 (2 - 16)
JDMAI5	0-40	21.4 (15.8 - 27)	23.9 (19 - 27.8)	6.5 (1 - 18)
JDMAI6	0-39	21.3 (17.3 - 28)	24.5 (20 - 28.6)	8.5 (2 - 17)

IQR = Interquartile Range.

***Construct validity*.** The Spearman's correlations between the six versions of the JDMAI and the JDM clinical measures not included in the score are shown in **Table 5**. In the PRINTO sample, correlations for JDMAI were high with muscle activity VAS, DAS total and CHAQ, moderate-to-high with MMT8, CMAS and hMC, moderate with skin activity VAS, DAS muscle, DAS skin, pain VAS and CHQ-PhS, and low with CK, MDI, and CHQ-PsS. In the JDM trial sample, correlations were

moderate-to-high with DAS total, MMT8, and hMC, moderate with muscle activity VAS, DAS muscle, CMAS, pain VAS, and CHAQ, low-to-moderate with skin activity VAS, DAS skin, CHQ-PhS, and CHQ-PsS, and low with CK and MDI. In the Routine sample, correlations were high with muscle activity VAS, skin activity VAS, DAS total, DAS muscle, DAS skin, MMT8, CMAS and hMC and moderate with CK, pain VAS and fatigue VAS. Correlations were overall in line with prediction, but were higher for the Routine sample than for the other two datasets.

Table 5. Spearman's Rank correlation between the six versions of the JDMAI and JDM outcome measures.

	JDMAI1	JDMAI2	JDMAI3	JDMAI4	JDMAI5	JDMAI6
PRINTO sample						
Muscle activity VAS	0.75	0.76	0.74	0.75	0.77	0.78
Skin activity VAS	-	0.45	-	0.46	-	0.42
DAS total	0.72	0.77	0.71	0.77	0.72	0.77
DAS muscle	0.64	0.68	0.64	0.68	0.66	0.69
DAS skin	0.42	-	0.43	-	0.41	-
MMT8	-0.70	-0.74	-	-	-0.66	-0.69
CMAS	-0.69	-0.75	-0.68	-0.74	-	-
hMC	-	-	-0.71	-0.76	-0.68	-0.72
Creatine kinase	0.26	0.28	0.26	0.28	0.28	0.30
MDI	0.23	0.20	0.23	0.20	0.21	0.18
Pain VAS	0.49	0.52	0.48	0.51	0.49	0.52
CHAQ	0.72	0.77	0.72	0.77	0.75	0.79
CHQ Phs	-0.61	-0.65	-0.60	-0.64	-0.62	-0.66
CHQ PsS	-0.22	-0.22	-0.23	-0.23	-0.22	-0.21

JDM trial sample						
Muscle activity VAS	0.65	0.63	0.62	0.6	0.66	0.64
Skin activity VAS	-	0.39	-	0.42	-	0.39
DAS total	0.67	0.71	0.63	0.67	0.70	0.74
DAS muscle	0.56	0.59	0.51	0.54	0.62	0.64
DAS skin	0.35	-	0.36	-	0.34	-
MMT8	-0.69	-0.72	-	-	-0.62	-0.64
CMAS	-0.65	-0.68	-0.60	-0.63	-	-
hMC	-	-	-0.70	-0.74	-0.67	-0.71
Creatine kinase	0.25	0.25	0.23	0.24	0.27	0.27
MDI	-0.08	-0.11	-0.05	-0.08	-0.07	-0.09
Pain VAS	0.45	0.48	0.44	0.48	0.47	0.5
CHAQ	0.48	0.51	0.46	0.48	0.51	0.54
CHQ PhS	-0.39	-0.40	-0.37	-0.39	-0.42	-0.44
CHQ PsS	-0.33	-0.33	-0.32	-0.33	-0.36	-0.35
Routine sample						
Muscle activity VAS	0.87	0.87	0.88	0.88	0.87	0.87
Skin activity VAS	-	0.88	-	0.86	-	0.89
DAS total	0.91	0.95	0.90	0.95	0.90	0.95
DAS muscle	0.79	0.81	0.76	0.82	0.8	0.82
DAS skin	0.75	-	0.71	-	0.73	-
MMT8	-0.82	-0.83	-	-	-0.79	-0.81
CMAS	-0.81	-0.8	-0.81	-0.8	-	-
hMC	-	-	-0.84	-0.84	-0.83	-0.83
Creatine kinase	0.44	0.42	0.45	0.41	0.44	0.42
Pain VAS	0.65	0.65	0.65	0.65	0.64	0.63
Fatigue VAS	0.65	0.65	0.64	0.63	0.65	0.64

Internal consistency. Cronbach's alpha values were fair-to-moderate in the PRINTO sample, slight-to-poor in the JDM trial sample, and substantial in the Routine sample (see **Table 6**). That the internal consistency was lower in the PRINTO and JDM trial samples than in the Routine dataset could depend on the difference in the state of the disease, which was active, and, thus, likely more variable, in all patients included in the former datasets and overall more stable in patients followed in routine care.

Table 6. Cronbach's alpha value of internal consistency for the six JDMAI versions in the three patient datasets.

	PRINTO sample	JDM trial sample	Routine sample
JDMAI1	0.69	0.62	0.89
JDMAI2	0.69	0.59	0.87
JDMAI3	0.69	0.62	0.88
JDMAI4	0.69	0.58	0.85
JDMAI5	0.70	0.62	0.88
JDMAI6	0.70	0.58	0.86

Exploratory factor analysis. Exploratory factor analysis of JDMAI led to the unambiguous identification of two separate factors: one factor incorporated muscle strength assessment, PhGA and PaGA; the second factor incorporated skin assessment (**Table 7**).

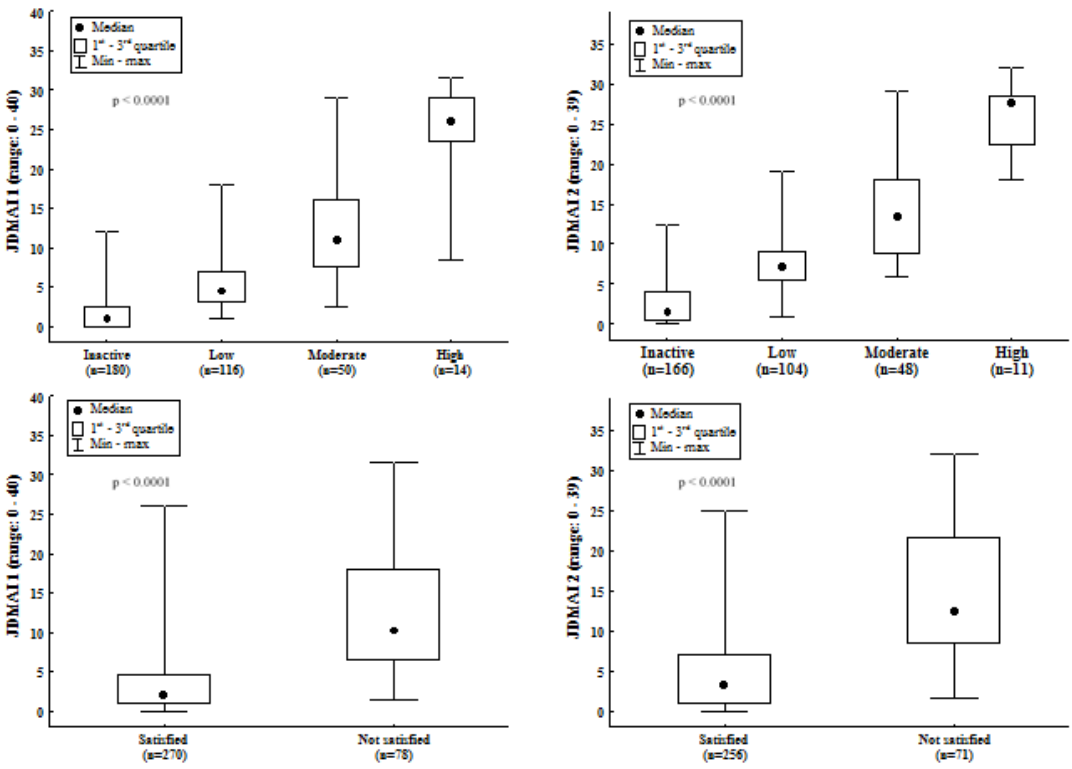
Table 7. Results of exploratory factor analysis in the JDM trial sample.

	N° of factors	Correlation between factors	Factors	Components (loadings)
JDMAI1	2	0.3	1	hMC (0.8) PhGA (0.5) PaGA (0.5)
			2	Skin VAS (0.6)
JDMAI2	2	0.1	1	hMC (0.8) PhGA (0.7) PaGA (0.6)
			2	Skin DAS (0.4)
JDMAI3	2	0.4	1	MMT8 (0.8) PhGA (0.5) PaGA (0.5)
			2	Skin VAS (0.6)
JDMAI4	2	0.13	1	MMT8 (0.7) PhGA (0.7) PaGA (0.6)
			2	Skin DAS (0.4)
JDMAI5	2	0.3	1	CMAS (0.9) PhGA (0.6) PaGA (0.5)
			2	Skin VAS (0.6)
JDMAI6	2	0.1	1	CMAS (0.8) PhGA (0.7) PaGA (0.5)

	2	Skin DAS (0.5)

Discriminant validity. The JDMAI showed strong ability to discriminate patients judged as being in the states of inactive disease or low, moderate or high disease activity by the physician ($p < 0.001$). The JDMAI discriminated well between patients whose parents were satisfied or not satisfied with the course of their child's illness ($p < 0.001$) (see **Figure 1** for the results regarding JDMAI1 and JDMAI2). For complete results see the Appendix (page 46 onward).

Figure 1. Assessment of the ability of JDMAI1 and JDMAI2 to discriminate patients judged as being in the states of inactive disease or low, moderate or high disease activity by the physician, and between patients whose parents were satisfied or not satisfied with the course of their child's illness in the Routine sample.



Responsiveness to change. In the JDM trial sample, the SRM values were good for both responders and non-responders, although greater for the former group (2.9-3.1 vs 1.0-1.1). In the Routine sample, the SRM was good (0.8–1.1) in patients judged as improved and moderate (0.7–0.8) in patients judged as not improved. SRM values were similar across JDMAI versions (see **Table 8** and **Table 9**).

Table 8. Standardized response mean of the six JDMAI versions in patients classified as responders or non-responders at 6 months in the JDM trial sample.

	Responders	Non responders
JDMAI1	3.07	1.06
JDMAI2	2.97	1.00
JDMAI3	3.12	1.08
JDMAI4	3.00	1.00
JDMAI5	2.96	1.08
JDMAI6	2.90	0.97

Table 9. Standardized response mean of the six JDMAI versions in patients judged subjectively as improved or not improved after 6 months of follow-up by the caring physician in the Routine sample.

	Improved	Not improved
JDMAI1	1.06	0.78
JDMAI2	0.97	0.71

JDMAI3	1.14	0.79
JDMAI4	1.07	0.71
JDMAI5	0.92	0.74
JDMAI6	0.82	0.71

Discussion

We have described herein the development of the first composite disease activity score for JDM and provided preliminary evidence of its validity. The JDMAI combines the four key measures of disease activity in JDM (PhGA, PaGA, muscle strength and skin disease activity) into a single continuous measure. The score of the JDMAI results from the arithmetic sum of the scores of each individual component, which makes its calculation simple and quick. The PhGA and PaGA are both measured on a VAS, which is preferentially measured on a 21-numbered circle scale [45]. Because there are no universally agreed instruments to quantify muscle strength and skin disease in JDM, we tested six different versions of the JDMAI, which included three muscle strength measures (MMT8, CMAS and hMC) and two skin assessment scales (a skin disease activity VAS and the skin component of the DAS). To make the score of the three muscle strength tools consistent and reduce the potential that it might dominate the composite index, the score of the three instruments was converted to a 0-10, decile-based, scale. Also for sake of consistency, scores were reversed to give them the same direction (i.e. 0 = best to 10 = worst) as the other JDMAI components.

Validation procedures were conducted on three multinational datasets, comprising a total of 627 patients included in a research study, in a randomized clinical trial, or followed up during routine clinical care. Altogether, these patients are likely representative of the entire spectrum of children with JDM seen in paediatric rheumatology centres worldwide. In validation analyses, the JDMAI was found to possess face and content validity, good construct validity, satisfactory internal consistency, fair responsiveness to clinically important change over time and strong discriminative validity. Importantly, though not unexpectedly, exploratory factor analysis showed that both PhGA and PaGA are mostly driven by the severity of muscle impairment, and that skin disease constitutes a separate disease domain. This finding suggests the need for future evaluations of the relative impact of muscle and skin symptoms on physician's and parent's (and patient's) perception of disease burden. The high SRM values in responders in the JDM trial sample suggest that the JDMAI is potentially applicable in therapeutic studies. That construct validity and internal consistency were greater in the Routine dataset indicate that it is also suited for use in daily practice.

Overall, the six versions of the JDMAI showed similar performance in validation analyses. They can, therefore, be considered equally suitable and reliable. However, there are some differences in the measures utilized for the assessment of muscle strength and skin disease that are worth emphasizing. The MMT8, included in JDMAI3 and JDMAI4, and the CMAS, included in JDMAI5 and JDMAI6, are established key measures of muscle strength in children with JDM [11, 12]. However, it has been argued that both instruments have limitations: the MMT8 lacks assessment of abdominal muscles, which are a major site of muscle

disease in JDM, and the CMAS is lengthy and requires proper equipment to complete the entire test. We have recently devised and tested a hybrid measure of muscle strength for JDM (the hMC), which combines the whole MMT8 with 3 of the 14 items of the CMAS and is thought to be more complete than the MMT8 and more feasible than the CMAS [30]. This tool is included in JDMAI1 and JDMAI2.

Several measures have been proposed to assess skin disease in JDM, including the original and abbreviated Cutaneous Assessment Tool (CAT) [46, 47], the DAS skin [27], the Myositis Intention to Treat Activity Index (MITAX) [31], and the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) [48]. However, none of these tools have been universally embraced [49]. We opted for the DAS skin (included in JDMAI2, JDMAI4 and JDMAI6) and VAS skin (included in JDMAI1, JDMAI3 and JDMAI5) because we thought they were most suitable in terms of ease of use and quantitative measurement properties. Notably, the VAS has the advantage of being expressed on the same 0-10 scale as the other JDMAI items, whereas the DAS skin score ranges from 0 to 9. It is, however, anticipated that the JDMAI might need to be revised when new well-designed and validated skin-specific instruments for JDM will become available [50]. In the meantime, we favour the JDMAI1, as it includes a feasible muscle strength tool and the simplest skin assessment measure.

This study has some limitations. We recognize that the new tool was developed by a restricted group of experts based on their experience in the assessment of children with JDM and the review of the pertinent literature and that a formal Delphi survey was not carried out. The JDMAI assesses specifically

the two major systems affected in JDM (skeletal muscles and skin), but neglects other potentially, though less commonly, involved organs/systems, such as the gastrointestinal, pulmonary and cardiac. It is, however, assumed that active disease in these organs is incorporated, at least in part, in PhGA and PaGA. In the Routine dataset, the proportion of patients with constitutional features and articular, pulmonary, gastrointestinal and cardiac involvement was 89.6%, 46.6%, 17.8%, 16.2% and 3.7%, respectively. This information was not available for the other two datasets. We acknowledge that the choice to transform muscle score values in deciles is arbitrary and that its validity should be further tested. The design of the study did not allow us to test the inter- and intra-observer reliability of the JDMAI. This property was, however, demonstrated for all individual measures included in the tool [11, 12]. Due to the lack of longitudinal assessments, we could not investigate the capacity of the JDMAI to predict disease outcomes, such as continued activity, cumulative damage, or functional disability.

In conclusion, we have developed a new composite disease activity score for JDM, which is composed of the four key disease activity measures for this disease. In validation analyses, the instrument was found to possess good measurement properties, which indicates that it is applicable in both clinical and research settings. The final version of the JDMAI will be selected after its prospective validation, which is currently under way. Another key objective of future analyses is to define cutoffs in the score that correspond to the states of inactive disease and low, moderate and high disease activity in JDM.

THIRD PART: PRELIMINARY PROSPECTIVE VALIDATION OF THE JUVENILE DERMATOMYOSITIS ACTIVITY INDEX (JDMAI)

Introduction

In parallel to the large scale validation carried out on the multinational sample of patients so far described, a prospective validation of the new tool has been conducted on a sample of JDM patients seen in clinical practice and specifically enrolled for the purpose of this study.

Patients and Methods

A total of 57 JDM patients, either at disease onset or at a follow-up visit, a median of 2 years after disease onset, were consecutively enrolled. Each patient received a retrospective assessment and a cross-sectional evaluation at study entry. Twenty-five patients also underwent a second (prospective) assessment after a median of 3.6 months from study entry. Nearly half of the patients (to be precise, 30), were evaluated by the examinee between October 2015 and March 2016, during her fellowship spent at the Rheumatology Department of Great Ormond Street Hospital in London. The rest of the patients were enrolled by the candidate herself from October 2016 onward, at the Rheumatology Department of Istituto Giannina Gaslini in Genoa, mostly when admitted to the ward.

At every study visit, the following evaluations were collected:

a) demographic data: sex, birth date, disease onset date, date of first visit at the centre for JDM, date of study visit;

b) retrospective data: JDM diagnostic criteria that were present at the time of diagnosis, date of diagnosis, main disease manifestations prior to study visit, patient drug therapy prior to study visit, Myositis Specific Antibodies (MSA) and Antinuclear Antibodies (ANA) status;

c) cross-sectional data, as follows:

- muscle disease activity assessment: MMT8, CMAS, hMC, muscular domain of DAS, muscle VAS;

- skin disease activity assessment: skin domain of DAS, skin VAS, a modified version of the skin section of the Myositis Intention to Treat Activity Index or MITAX (considering all its original 11 items but evaluating them in a quantitative instead of in a categorical way - namely, on a 0-4 scale where: 0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe);

- physician's global assessment of overall disease activity (PhGA) on a visual analogue scale (VAS) (where 0 = no activity and 10 = maximum activity);

- evaluation of disease status by the physician (inactive disease/continued activity/flare - if continued activity/flare: level of disease activity, defined as minimal, moderate or high);

- evaluation of disease course from previous visit by the physician (much improved/slightly improved/stable-unchanged/slightly worsened/much worsened/1st visit);

- laboratory results: CK, LDH, ALT, AST, ESR;

- a detailed record of patient drug therapy at study visit;

- evaluation of cumulative damage through the Myositis Damage Index (MDI).

Parent-reported outcomes were collected through the administration of a multidimensional questionnaire taking into account the following items: functional ability, pain VAS, fatigue VAS, symptoms in the last four weeks, global evaluation of disease activity, evaluation of disease status from previous visit, evaluation of disease course from previous visit, ongoing therapies and possible side effects, compliance to treatments, possible school problems, quality of life, parent's global assessment of patient's overall wellbeing (PaGA) on a VAS (where 0 = best and 10 = worst), and the so called "parent acceptable symptom state" (PASS) [43]. If appropriate (that is, above 7-8 years of age), the same questionnaire was administered to patients as well.

Similarly to what already done during the preliminary validation phase of the new tool, the construct validity, internal consistency, responsiveness to change, and discriminant ability of the six different versions of the JDMAI were assessed on the prospective sample of patients. Validation of the JDMAI in this sample was conducting according to the same procedures described in the Second

Part of the work (see page 14 for details).

Results

The main demographic and clinical features of the prospective sample at baseline are shown in **Table 10**, while **Table 11** shows patients' treatment history up to baseline visit.

Table 10. Demographic and clinical features of the prospective sample (at baseline).

	Score Range Min – Max	Prospective sample N = 57 Median (IQR)
Sex (Female) - n. (%)	-	31 (54.4%)
Caucasian, yes - n. (%)	-	48 (84.2%)
ANA, positive - n. (%)	-	15/23 (65.2%)
MSA, positive - n. (%)	-	12/18 (66.7%)
Age at disease onset (years)	-	5.7 (2.9 - 8.2)
Age at diagnosis (years)	-	6.4 (3.7 - 8.6)
Age at 1st visit (years)	-	8.6 (6.2 - 11.8)
Disease duration from onset to study visit (years)	-	2 (0.6 - 4.5)
Physician Global Activity VAS	0-10	2 (0.7 - 3.6)
Muscle activity VAS	0-10	0.5 (0 - 4)
Skin activity VAS	0-10	1.5 (0.5 - 2.9)
DAS - muscle section	0-11	2.5 (0 - 5)

DAS - skin section	0-9	5 (4 - 5)
DAS Total score	0-20	7 (4 - 11)
MMT8	0-80	76 (66 - 80)
CMAS	0-52	48 (39 - 52)
hMC	0-100	91.5 (79 - 100)
ESR, mm/h	0-10*	8.9 (5 - 21.1)
Creatine Kinase, U/L	0 – 150*	69 (5.8 - 124)
Lactate Dehydrogenase	84-480*	441 (241.5 - 667)
Alanine Transaminase	0-40*	33 (21 - 50)
Aspartate Transaminase	0-40*	43.4 (28.6 - 57)
MDI	0-35	0 (0 - 1)
MDI: 0 *(n, %)*		*19/27 (70.4%)*
1-2 *(n, %)*		*4/27 (14.8%)*
≥ 3 to 8 *(n, %)*		*4/27 (14.8%)*
Parent Global Assessment (VAS)	0-10	3 (0.6 - 5.9)
Pain VAS	0-10	1 (0 - 4)
Fatigue VAS	0-10	2.5 (0 - 7.5)
PASS, yes *(n, %)*		*8/23 (34.8%)*

* Normal values of the corresponding laboratory analysis; IQR = Interquartile Range; NA = Not Available.

Table 11. Treatment history up to baseline visit.

	Prospective sample (N = 57)
	n. (%)
Oral corticosteroids	43 (75.4%)

Intravenous corticosteroids	6 (10.5%)
Corticosteroids pulses	30 (52.6%)
Oral Cyclophosphamide	3 (5.7%)
Intravenous Cyclophosphamide	11 (19.3%)
Oral Methotrexate	11 (19.3%)
Subcutaneous Methotrexate	38 (66.7%)
Oral Cyclosporin	9 (15.8%)
Intravenous Infliximab	7 (12.3%)
Intravenous Rituximab	3 (5.3%)
Intravenous Immunoglobulin	21 (36.8%)
Oral Hydroxicloroquine	18 (31.6%)
Oral Azathioprine	6 (10.5%)
Other	5 (8.8%)

The following table (**Table 12**) demonstrates the descriptives of the 6 versions of JDMAI at baseline.

Table 12. Descriptives of the 6 versions of JDMAI at baseline.

	Score range (min – max)	Median (IQR)
JDMAI-1	0 - 40	8.4 (2.8 - 14.4)
JDMAI-2	0 - 39	11 (5.5 - 17.9)
JDMAI-3	0 - 40	8.4 (2.8 - 14.4)

JDMAI-4	0 - 39	11.2 (5.5 - 17.9)
JDMAI-5	0 - 40	8.1 (2.8 - 14.4)
JDMAI-6	0 - 39	11 (5.5 - 17.9)

IQR = Interquartile Range.

***Construct validity*.** Spearman's correlations between the six versions of the JDMAI and the JDM clinical measures not included in the score are shown in **Table 13**. In the prospective sample, correlations for JDMAI were high with muscle activity VAS, DAS muscle, DAS total, pain VAS, and fatigue VAS. The correlations with the skin index not contained in the specific version of the tool itself (that is, skin VAS or cutaneous domain of DAS) turned out to be high as well. As expected, JDMAI correlations with laboratory parameters and MDI came out to be moderate-to-low.

Table 13. Spearman's Rank correlation between the six different versions of the JDMAI and the main JDM outcome measures at baseline.

	JDMAI1	JDMAI2	JDMAI3	JDMAI4	JDMAI5	JDMAI6
Muscle activity VAS	0.84	0.84	0.83	0.84	0.84	0.84
Skin activity VAS	-	0.76	-	0.76	-	0.75
DAS - muscle section	0.79	0.80	0.78	0.79	0.79	0.79
DAS - skin section	0.72	-	0.74	-	0.72	-
Disease Activity Score (DAS)	0.87	0.89	0.86	0.88	0.86	0.88
MMT 8	-0.84	-0.85	-	-	-0.83	-0.83
CMAS	-0.79	-0.79	-0.77	-0.77	-	-

Hybrid MMT/CMAS (hMC)	-	-	-0.82	-0.83	-0.83	-0.83
Creatine kinase, U/L	0.21	0.21	0.2	0.22	0.23	0.23
LDH, U/L	0.5	0.49	0.49	0.5	0.52	0.52
ALT, U/L	0.44	0.43	0.42	0.43	0.45	0.45
AST, U/L	0.49	0.48	0.48	0.48	0.49	0.48
ESR, mm/h	0.38	0.35	0.38	0.35	0.37	0.35
MDI	-0.04	-0.05	-0.04	-0.05	-0.05	-0.05
Pain VAS	0.74	0.71	0.74	0.74	0.73	0.73
Fatigue VAS	0.88	0.89	0.88	0.88	0.89	0.89

Internal consistency. Cronbach's alpha values turned out to be very high (0.884-0.900) for all versions of JDMAI (see **Table 14** for complete results).

Table 14. Internal consistency: Cronbach's Alpha (baseline visit).

	Prospective sample
JDMAI 1	0.897
JDMAI 2	0.884
JDMAI 3	0.900
JDMAI 4	0.890
JDMAI 5	0.899
JDMAI 6	0.884

Responsiveness to change. In the prospective patient sample, the SRM values were greater for the patients judged as improved by the physician or the

parent (SRM = 0.83-1.15) than for the ones judged as not improved or stable (SRM = 0.02-0.51). These results are shown in **Table 15**.

Table 15. Standardized response mean (SRM) of different JDMAI versions in all patients and in the patients judged as improved according to the physician's and parents' opinion in the Prospective sample after a median of 3.6 months of follow-up.

	All patients	Physician's opinion		Parents' opinion	
		Improved	Worsened/Stable	Improved	Worsened/Stable
JDMAI 1	0.8	1.07	0.02	0.89	0.49
JDMAI 2	0.76	1.12	0.21	0.87	0.37
JDMAI 3	0.8	1.08	0.02	0.96	0.51
JDMAI 4	0.78	1.15	0.21	0.93	0.40
JDMAI 5	0.78	1.04	0.02	0.84	0.44
JDMAI 6	0.74	1.07	0.21	0.83	0.33

Discriminant ability. The JDMAI showed strong ability to discriminate patients judged as being in the states of inactive disease or low, moderate or high disease activity by the physician ($p < 0.001$) or by the parent ($p = 0.011$-0.031). See **Table 16**, **Table 17** and **Table 18** for details. The JDMAI discriminated well between patients whose parents were satisfied or not satisfied of the course of their child's illness ($p \leq 0.001$). These results are shown in **Table 19**.

Table 16. Assessment of the ability of different JDMAI versions to discriminate patients judged as being in the states of continuous activity/flare or inactive disease by the physician in all visits in the Prospective dataset in which this evaluation was available (n=69).

		N	Median [IQR]	Min - Max	P
JDMAI 1	Continuous activity/flare	56	9.9 [5.3 - 14.4]	2.5 - 29.8	< 0.0001
	Inactive	19	1.3 [0.7 - 2.2]	0 - 7.7	
JDMAI 2	Continuous activity/flare	56	12.6 [8.3 - 17.7]	4 - 30.1	< 0.0001
	Inactive	19	4.3 [2.7 - 5]	0 - 10	
JDMAI 3	Continuous activity/flare	57	9.8 [5.5 - 14.4]	2.5 - 29.8	< 0.0001
	Inactive	19	1 [0.4 - 2]	0 - 7.7	
JDMAI 4	Continuous activity/flare	57	12.2 [9.1 - 17.5]	4 - 30.1	< 0.0001
	Inactive	19	4 [2.5 - 5]	0 - 10	
JDMAI 5	Continuous activity/flare	56	10.1 [5.1 - 14.2]	2.5 - 31	< 0.0001
	Inactive	19	1.3 [0.7 - 2.5]	0 - 7.7	
JDMAI 6	Continuous activity/flare	56	13.2 [8.2 - 17.5]	4 - 32.5	< 0.0001
	Inactive	19	4.3 [2.7 - 5]	0 - 10	

IQR = Interquartile Range; P: Non parametric test: Mann-Whitney *U* test.

Table 17. Assessment of the ability of different JDMAI versions to discriminate patients judged as being in the states of persistent activity/relapse or remission

by the parents' evaluation in all visits in the Prospective dataset in which this evaluation was available (n=29).

		N	Median [IQR]	Min - Max	P
JDMAI 1	Persistent activity/relapse	26	10.6 [5 - 14]	1.6 - 28	0.016
	Remission	9	2.5 [1 - 6.5]	0 - 15	
JDMAI 2	Persistent activity/relapse	26	12.8 [8.5 - 16.5]	4 - 29.5	0.031
	Remission	9	6.5 [2.5 - 10.2]	0 - 18	
JDMAI 3	Persistent activity/relapse	27	9.5 [5 - 14]	1.6 - 27	0.011
	Remission	9	2.5 [0.5 - 5.5]	0 - 15	
JDMAI 4	Persistent activity/relapse	27	12 [8.5 - 16]	4 - 28.5	0.027
	Remission	9	5.5 [2.5 - 9.2]	0 - 18	
JDMAI 5	Persistent activity/relapse	26	10.6 [5 - 14]	1.6 - 31	0.013
	Remission	9	2.5 [1 - 5.5]	0 - 15	
JDMAI 6	Persistent activity/relapse	26	13.3 [8.3 - 16.5]	4 - 32.5	0.029
	Remission	9	6.5 [2.5 - 9.2]	0 - 18	

IQR = Interquartile Range; P: Non parametric test: Mann-Whitney *U* test.

Table 18. Assessment of the ability of different JDMAI versions to discriminate patients judged as being in the states of high, moderate, minimal, or inactive disease by the physician in all visits in the Prospective dataset in which this evaluation was available (n=69).

	N	Median [IQR]	Min - Max	p

JDMAI 1	High disease activity	4	26.5 [22.7 - 28]	20.5 - 28	< 0.0001
	Moderate disease activity	29	12.7 [8.4 - 16.7]	2.7 - 29.8	
	Minimal disease activity	23	5.5 [4 - 9.4]	2.5 - 13.5	
	Inactive	19	1.3 [0.7 - 2.2]	0 - 7.7	
JDMAI 2	High disease activity	4	28.6 [25.4 - 29.4]	22.8 - 29.5	< 0.0001
	Moderate disease activity	29	15 [11.5 - 19.8]	5.5 - 30.1	
	Minimal disease activity	23	8.5 [6.6 - 12.2]	4 - 17	
	Inactive	19	4.3 [2.7 - 5]	0 - 10	
JDMAI 3	High disease activity	4	26 [22.2 - 27]	19.5 - 27	< 0.0001
	Moderate disease activity	29	12.6 [8.4 - 15.7]	2.7 - 29.8	
	Minimal disease activity	24	5.9 [4 - 8.5]	2.5 - 13.5	
	Inactive	19	1 [0.4 - 2]	0 - 7.7	
JDMAI 4	High disease activity	4	27.8 [24.4 - 28.9]	21.8 - 29.2	< 0.0001
	Moderate disease activity	29	15.5 [12 - 18.8]	5.5 - 30.1	
	Minimal disease activity	24	9 [6.6 - 11.5]	4 - 17	
	Inactive	19	4 [2.5 - 5]	0 - 10	
JDMAI 5	High disease activity	4	26.5 [22.7 - 30]	21.5 - 31	< 0.0001
	Moderate disease activity	29	12.4 [8.1 - 15.7]	2.7 - 30.8	
	Minimal disease activity	23	5.2 [4 - 9.8]	2.5 - 13.5	
	Inactive	19	1.3 [0.7 - 2.5]	0 - 7.7	
JDMAI 6	High disease activity	4	28.6 [26 - 30.8]	23.8 - 32.5	< 0.0001
	Moderate disease activity	29	15.5 [11.5 - 18.8]	5.5 - 31.1	
	Minimal disease activity	23	8.3 [6.6 - 11.4]	4 - 17	

	Inactive	19	4.3 [2.7 - 5]	0 - 10

IQR = Interquartile Range; P: Non parametric analysis of variance: Kruskal-Wallis test.

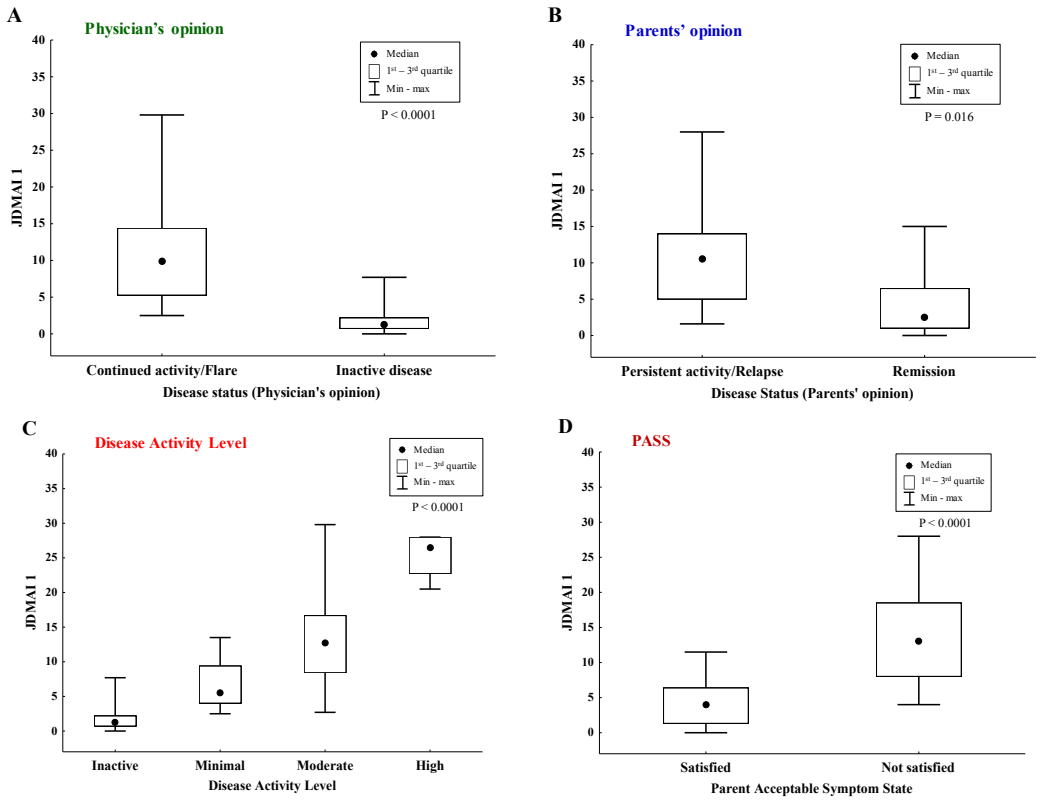
Table 19. Assessment of the ability of different JDMAI versions to discriminate between patients whose parents were not satisfied or satisfied with the course of their child's illness in all visits in the Prospective dataset in which this evaluation was available (n=29).

		N	Median [IQR]	Min - Max	P
JDMAI 1	Not satisfied	19	13 [8 - 18.5]	4 - 28	< 0.0001
	Satisfied	16	4 [1.3 - 6.4]	0 - 11.5	
JDMAI 2	Not satisfied	19	15 [11.5 - 22]	4.5 - 29.5	0.0001
	Satisfied	16	6.5 [4.2 - 9.8]	0 - 15.5	
JDMAI 3	Not satisfied	19	13 [8 - 18.5]	3.8 - 27	< 0.0001
	Satisfied	17	4 [1.6 - 6.6]	0 - 11.5	
JDMAI 4	Not satisfied	19	15.5 [12 - 21.8]	4.5 - 28.5	0.0001
	Satisfied	17	6.5 [4.3 - 10.3]	0 - 15.5	
JDMAI 5	Not satisfied	19	13.5 [8 - 20.5]	4 - 31	< 0.0001
	Satisfied	16	4 [1.3 - 5.4]	0 - 12.5	
JDMAI 6	Not satisfied	19	16 [11.5 - 23.8]	4.5 - 32.5	< 0.0001
	Satisfied	16	6.5 [4.2 - 8.9]	0 - 15.5	

IQR = Interquartile Range; P: Non parametric test: Mann-Whitney *U* test.

The following figure (**Figure 2**) is the graphic representation of the ability of JDMAI1 to discriminate between patients judged as being in the state of continued activity/flare or inactive disease by the physician (panel A), between patients judged as being in the state of persistent activity/relapse or remission by the parent (panel B), between patients judged as being in the state of inactive disease or low, moderate or high disease activity by the physician (panel C), and between patients whose parents were satisfied or not satisfied with the course of their child's illness (panel D) in the prospective sample. The other versions of the tool revealed similar discriminant ability (see the Appendix for complete results, page 51 onward).

Figure 2. Capacity of the JDMAI1 to discriminate between activity states and parent satisfaction/non satisfaction.



Conclusions and possible future developments

Validation analyses conducted on this prospective sample of 57 patients followed up at two tertiary-care paediatric rheumatology centers confirmed that the JDMAI possesses good measurement properties and is a suitable and reliable tool for the assessment of disease activity in children with JDM not only in the research setting but also in clinical practice. Importantly, the new tool revealed a strong capacity to capture the improvement of disease activity over time.

Overall, the six versions of the new tool showed similar performance in validation analyses. These results are in line with what found during the preliminary validation phase of our work (see Second part of the present dissertation).

We are now planning to carry on a large-scale prospective validation of the new tool, thanks to the involvement of a large number of international centres that are part of the main paediatric rheumatology networks worldwide. Each center will be asked to enroll all consecutive and unselected patients meeting the Bohan and Peter criteria for JDM, seen consecutively within the first 6 months after the study start. Informed consent will be obtained from all study patients. Each patient enrolled should undergo a retrospective evaluation, based on the review of the clinical chart, and two cross-sectional assessments at least three months apart.

The aim of such a prospective collection of consecutive patients is mainly to select the final version of the JDMAI among the six preliminary ones proposed, based on the observed metrologic performance of these various versions in a large cohort of patients seen in standard clinical practice. The JDMAI is the first composite disease activity score for JDM, and combines information from 3 physician-centered measures and 1 parent/patient-centered measure into a continuous measure of inflammation. The score of the JDMAI results from the arithmetic sum of the scores of each individual component, which makes its calculation simple and quick. The JDMAI proved good measurement properties in preliminary validation analysis and is a valid instrument for the assessment of disease activity in JDM. Therefore, it is potentially applicable in standard clinical care, observational studies and clinical trials.

The overall prognosis of JDM has improved significantly over the last decades, but the long-term outcomes differs substantially from patient to patient, suggestive of distinct clinical phenotypes with variable responses to treatment. Early and aggressive therapy may prevent or stabilize organ damage and disease complications like calcinosis. High doses of corticosteroids remain the cornerstone of therapy along with other immunosuppressant therapies depending on disease severity and response. The general treatment goals now include elimination of active disease and normalization of physical function, so as to preserve normal growth and development, and to prevent long-term damage and deformities [9, 51].

These advances have increased the potential for achievement of disease remission or, at least, low levels of disease activity, and have consequently moved

the therapeutic aims increasingly toward attainment of inactive disease status, similarly to what already seen in other pediatric rheumatologic diseases, such as JIA [52]. For reliable documentation of the advances in therapeutic efficacy, there is a need for validated and clinically useful criteria that describe precisely the clinical states of remission or near-remission.

One approach to defining remission is based on the use of core sets of multiple criteria, such as those included in PRINTO preliminary definition of remission, according to which a patient is defined as *clinically inactive on/off therapy* if at least three of four of the following measures meet the proposed inactivity cut-offs: 1) CPK ≤ 150 IU, 2) CMAS ≥ 48, 3) MMT8 ≥ 78, and 4) Physician's Global VAS ≤0.2 [53]. However, achievement of a complete absence of any measurable sign of disease activity is infrequent in the clinical practice, particularly among patients with polycyclic or continuous disease course. This highlights the need for establishing a well-defined state of minimal disease activity as an intermediate state between high disease activity and remission, though very close to remission. The criteria for inactive disease [53] are based only on physician-reported outcomes and a muscle enzyme level, whereas parent proxy-reported and child self-reported outcomes are neglected. Hence, definition of remission may not adequately reflect the parent's and child's perception of the disease status. The need to know whether a therapeutic intervention leads to an acceptable state according to the parent or the child has led us to propose the concept of parent/child acceptable symptom state in JIA [43]; this concept can be similarly applied in JDM.

An alternative approach to the measurement of disease activity is based

on composite disease activity scores. To aid in the interpretation of scores in the JDMAI, cutoff values are needed for identifying the main disease activity states in JDM (i.e. clinically inactive disease, minimal disease activity, moderate disease activity, and high disease activity), similarly to what already done to aid in interpretation of scores of the Juvenile Arthritis Disease Activity Score (JADAS), a similar composite disease activity tool recently developed and validated for JIA [20]. These definitions, at present not available, may provide simple and intuitive reference values that can be used to monitor the disease course over time in an individual patient or to compare disease status across individual patients or patient groups. Furthermore, they may support decisions about enrollment into clinical trials as well as requirements for changes in therapies and for defining therapeutic goals.

However, we do not believe the cutoffs should be used to "diagnose" remission. Rather, they represent an additional clinical tool that, if applied regularly in daily practice, may allow tighter therapeutic control of disease, support the optimization of treatment on an individual patient basis, and help prevent the development of damage and physical disability. Studies in adult Rheumatoid Arthritis have shown that patient outcomes are improved if low levels of disease activity are aimed for by frequent adjustments of therapy according to quantitative indices [54-56]. These observations have led to suggest that the strategy of tight control, aiming for remission, is more important than the medication [57]. Similar considerations may be valid for JDM as well, as it is widely recognized that persistently active disease plays a major role in causing disease-related damage and physical functional disability.

The incorporation of the treat-to-target strategy in clinical trials requires the availability of validated and clinically useful criteria that describes accurately the clinical states of remission or near-remission. The JDMAI may be suitable to implement a treat-to-target approach in JDM aimed to achieve and maintain tight disease control, with treatment escalation if a target JDMAI score is not reached, and may serve as an effective primary outcome measure in a therapeutic trial in JDM.

The search for biomarkers in pediatric rheumatic diseases is attracting increased interest. As regards JDM, some evidence suggests that this condition may be classified according to the presence of myositis-specific autoantibodies and myositis-associated autoantibodies; these autoantibodies define fairly homogeneous groups of patients with similar clinical features, responses to therapy, and prognoses. To be noticed, no reliable biomarker of disease activity is currently available for JDM. In the coming years, the discovery of additional biomarkers and their incorporation in daily practice to predict disease outcome and response to therapy in individual patients could facilitate the adoption of a stratified approach to diagnosis and management, and ultimately lead to more rational and effective clinical care. Furthermore, use of biomarkers may potentially help to avoid invasive procedures, such as muscle biopsy in JDM [58]. While waiting for these advances to get real, the usefulness of a composite disease activity score like JDMAI, that is quickly and easily calculated, becomes even more evident, as we lack the availability of any surrogate biomarker of the level of disease activity in JDM.

APPENDIX

Appendix to the Second Part: PRELIMINARY VALIDATION OF THE JUVENILE DERMATOMYOSITIS ACTIVITY INDEX (JDMAI)

Table A1. Assessment of the ability of different JDMAI versions to discriminate patients judged as being in the states of inactive disease, continuous activity or flare by the physician in all visits in the Routine dataset in which this evaluation was available.

		N	Mean (SD)	Median [IQR]	Min - Max	P
JDMAI 1	Inactive	180	1.8 (2.3)	1 [0 - 2.5]	0 - 12	< 0.0001
	Continuous activity/flare	183	8.8 (7.2)	6.5 [3.5 - 11]	0.5 - 31.5	
JDMAI 2	Inactive	166	2.6 (2.8)	1.5 [0.5 - 4]	0 - 12.5	< 0.0001
	Continuous activity/flare	166	10.7 (6.8)	8.5 [6 - 13]	0.5 - 32	
JDMAI 3	Inactive	185	1.7 (2.3)	1 [0 - 2.5]	0 - 12	< 0.0001
	Continuous activity/flare	187	8.7 (7.1)	6.5 [3.5 - 10.5]	0 - 31	
JDMAI 4	Inactive	171	2.5 (2.9)	1.5 [0 - 4]	0 - 13.5	< 0.0001
	Continuous activity/flare	170	10.6 (6.8)	9 [6 - 13]	0 - 31.5	
JDMAI 5	Inactive	152	1.8 (2.3)	1 [0 - 2.5]	0 - 12	< 0.0001
	Continuous activity/flare	148	8.8 (7)	6.5 [4.5 - 11]	0.5 - 32.5	
JDMAI 6	Inactive	146	2.6 (2.9)	1.5 [0 - 4]	0 - 12	< 0.0001

	Continuous activity/flare	139	10.5 (6.7)	8.5 [6 - 12.5]	0.5 - 33	

IQR: Interquartile Range; P: Non parametric test: Mann-Whitney *U* test.

Table A2. Assessment of the ability of different JDMAI versions to discriminate patients judged as being in the states of inactive disease, low, moderate or high disease activity by the physician in all visits in the Routine dataset in which this evaluation was available.

		N	Mean (SD)	Median [IQR]	Min - Max	p
JDMAI 1	Inactive	180	1.8 (2.3)	1 [0 - 2.5]	0 - 12	< 0.0001
	Low disease activity	116	5.3 (3.2)	4.5 [3 - 7]	1 - 18	
	Moderate disease activity	50	12.4 (6.3)	11 [7.5 - 16]	2.5 - 29	
	High disease activity	14	24.8 (6)	26 [23.5 - 29]	8.5 - 31.5	
JDMAI 2	Inactive	166	2.6 (2.8)	1.5 [0.5 - 4]	0 - 12.5	< 0.0001
	Low disease activity	104	7.5 (3.6)	7.3 [5.5 - 9]	1 - 19	
	Moderate disease activity	48	14.3 (6.3)	13.5 [8.8 - 18]	6 - 29	
	High disease activity	11	25.9 (4.4)	27.5 [22.5 - 28.5]	18 - 32	
JDMAI 3	Inactive	185	1.7 (2.3)	1 [0 - 2.5]	0 - 12	< 0.0001
	Low disease activity	118	5.2 (3.2)	4.5 [3 - 7]	0 - 18.5	
	Moderate disease activity	52	12.3 (6.2)	11 [7.3 - 16]	2.5 - 29	
	High disease activity	14	24.8 (6.1)	25.8 [23.5 - 30]	8.5 - 31	
JDMAI 4	Inactive	171	2.5 (2.9)	1.5 [0 - 4]	0 - 13.5	< 0.0001
	Low disease activity	106	7.4 (3.6)	7 [5.5 - 9]	0 - 19	

	Moderate disease activity	50	14.1 (6.1)	13.3 [9.5 - 18]	6 - 29	
	High disease activity	11	26 (4.5)	27.5 [23.5 - 29]	17 - 31.5	
JDMAI 5	Inactive	152	1.8 (2.3)	1 [0 - 2.5]	0 - 12	< 0.0001
	Low disease activity	95	5.6 (3.3)	5 [3.5 - 7]	1 - 19	
	Moderate disease activity	41	12.6 (6.4)	11 [7.5 - 16.5]	4 - 30	
	High disease activity	9	26 (4.8)	26.5 [22.5 - 29]	19 - 32.5	
JDMAI 6	Inactive	146	2.6 (2.9)	1.5 [0 - 4]	0 - 12	< 0.0001
	Low disease activity	88	7.7 (3.6)	7.5 [5.5 - 9]	1 - 20	
	Moderate disease activity	40	14.1 (6.6)	12 [9 - 18.8]	5.5 - 30	
	High disease activity	8	25.3 (5.5)	24.5 [20.8 - 30.3]	18 - 33	

IQR = Interquartile Range; P: Non parametric analysis of variance: Kruskal-Wallis test.

Table A3. Assessment of the ability of different JDMAI versions to discriminate between patients whose parents were satisfied or not satisfied with the course of their child's illness in all visits in the Routine dataset in which this evaluation was available.

		N	Mean (SD)	Median [IQR]	Min - Max	p
JDMAI 1	Satisfied	270	3.3 (4)	2 [1 - 4.5]	0 - 26	< 0.0001
	Not satisfied	78	13.1 (8.4)	10.3 [6.5 - 18]	1.5 - 31.5	
JDMAI 2	Satisfied	256	4.5 (4.5)	3.3 [1 - 7]	0 - 25	< 0.0001
	Not satisfied	71	14.9 (8)	12.5 [8.5 - 21.5]	1.5 - 32	
JDMAI 3	Satisfied	275	3.3 (4.1)	2 [0.5 - 4.5]	0 - 27	< 0.0001

	Not satisfied	81	12.8 (8.4)	10 [6.5 - 18]	0.5 - 31	
JDMAI 4	Satisfied	261	4.4 (4.6)	3.5 [1 - 7]	0 - 26	< 0.0001
	Not satisfied	74	14.6 (8)	12 [8.5 - 19]	0.5 - 31.5	
JDMAI 5	Satisfied	224	3.5 (4.2)	2 [0.5 - 5]	0 - 24	< 0.0001
	Not satisfied	67	12.5 (8.1)	10 [6.5 - 17.5]	1.5 - 32.5	
JDMAI 6	Satisfied	218	4.6 (4.7)	3.5 [1 - 7]	0 - 23	< 0.0001
	Not satisfied	64	14 (7.9)	11.8 [8 - 19.3]	1.5 - 33	

IQR = Interquartile Range; P: Non parametric test: Mann-Whitney U test.

Figure A1. Graphic representation of the ability of JDMAI3, JDMAI4, JDMAI5, and JDMAI6 to discriminate patients judged as being in the states of inactive disease or low, moderate or high disease activity by the physician in the Routine sample.

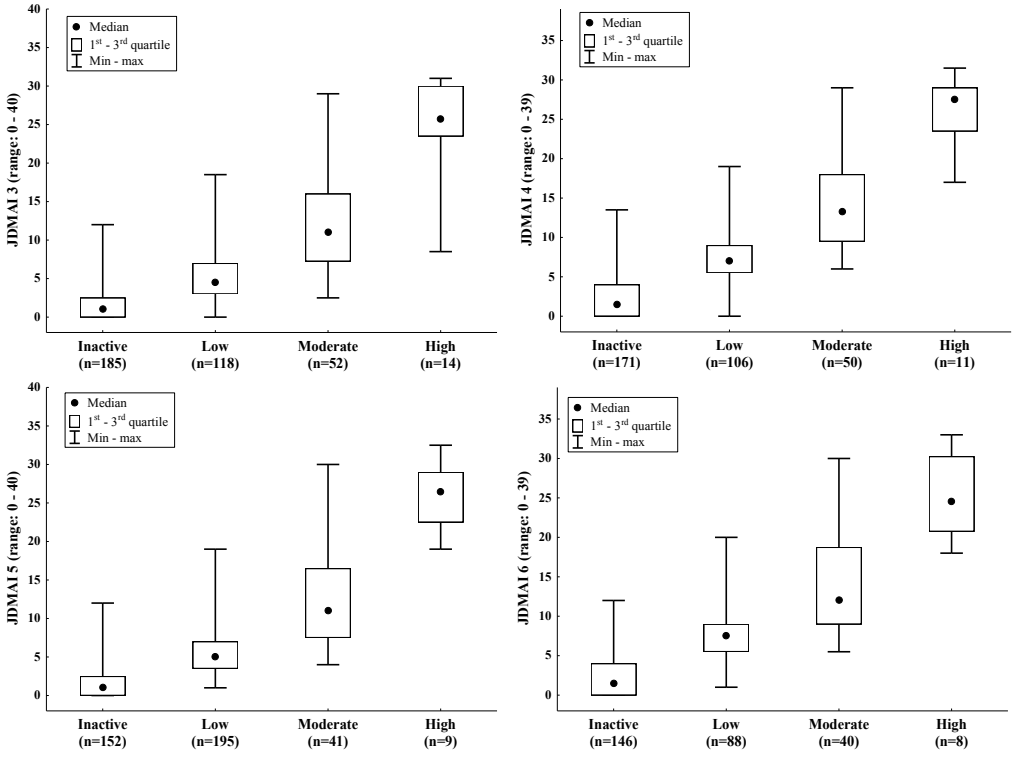
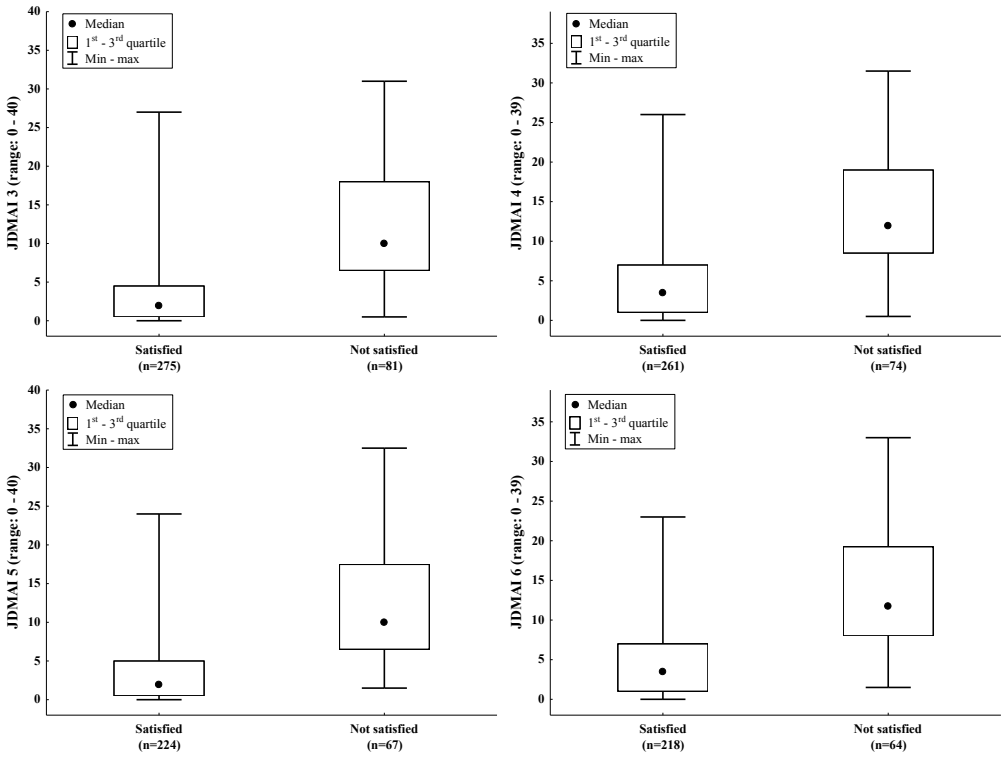
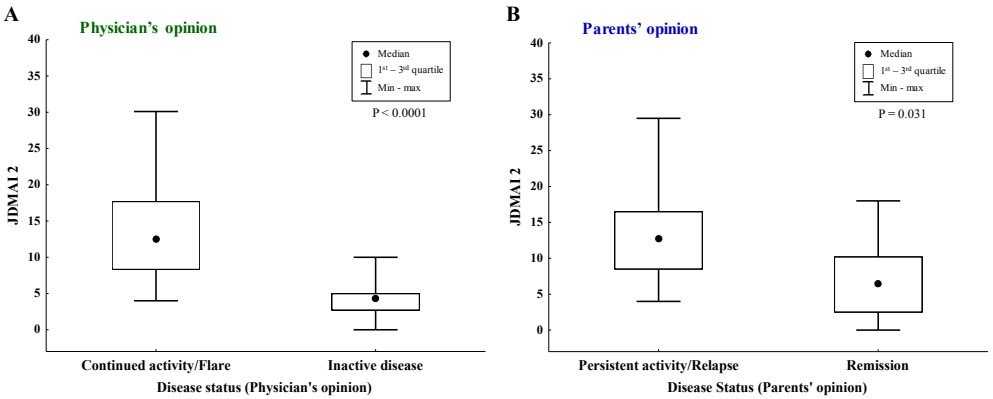


Figure A2. Graphic representation of the ability of JDMAI 3, JDMAI 4, JDMAI 5, and JDMAI6 to discriminate between patients whose parents were satisfied or not satisfied with the course of their child's illness in the Routine sample.



Appendix to the Third Part: PRELIMINARY PROSPECTIVE VALIDATION OF THE JUVENILE DERMATOMYOSITIS ACTIVITY INDEX (JDMAI)

Figure A3. Capacity of the JDMAI2 to discriminate between activity states and parent satisfaction/non satisfaction in the Prospective sample.



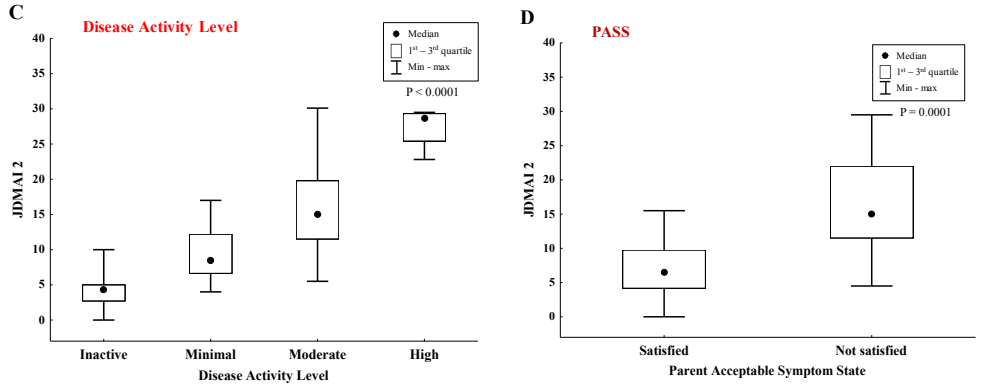


Figure A4. Capacity of the JDMAI3 to discriminate between activity states and parent satisfaction/non satisfaction in the Prospective sample.

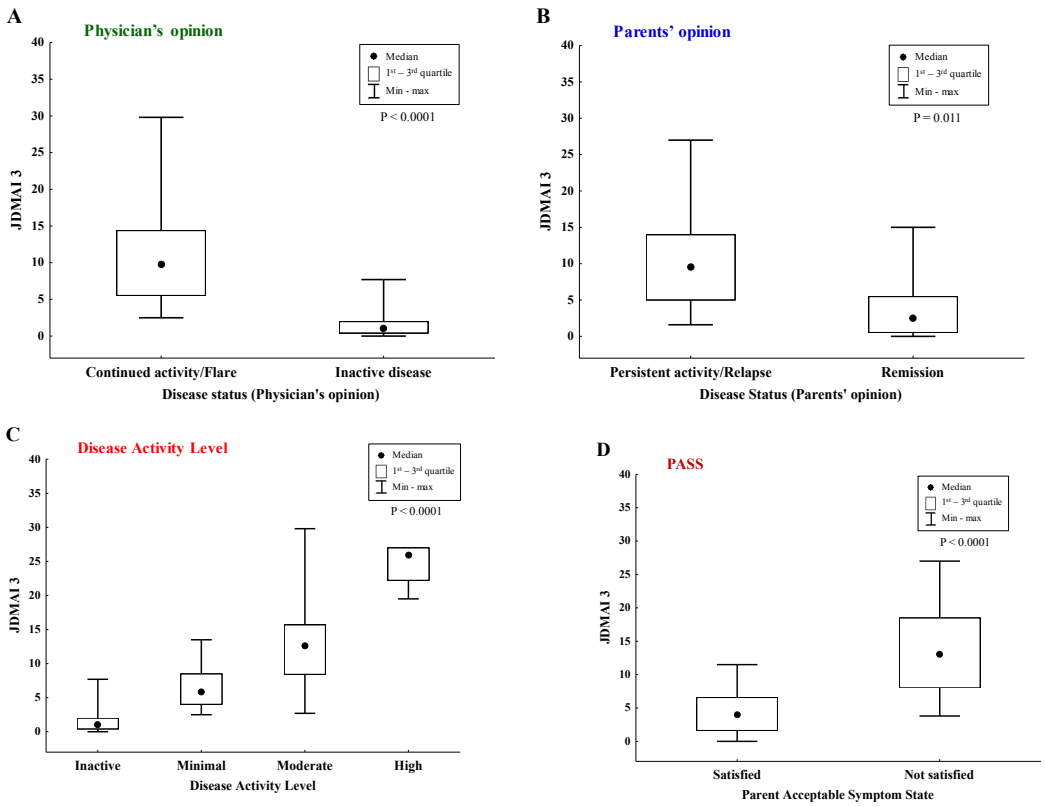
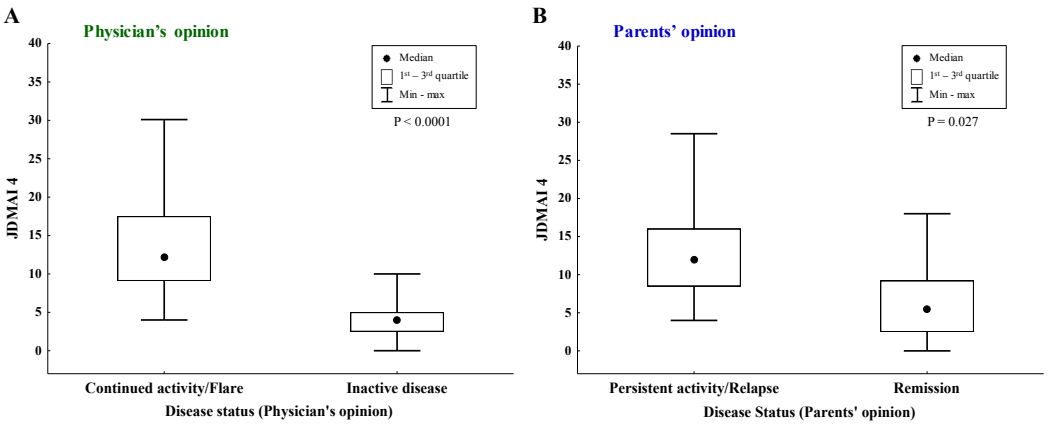


Figure A5. Capacity of the JDMAI4 to discriminate between activity states and parent satisfaction/non satisfaction in the Prospective sample.



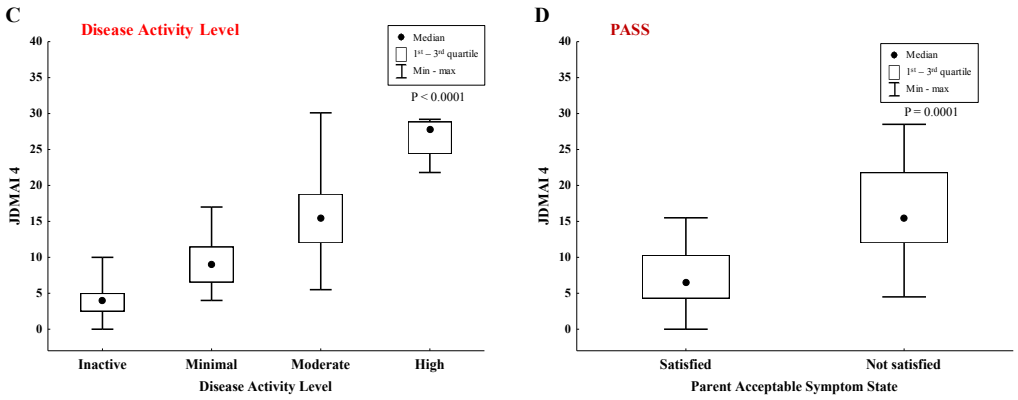


Figure A6. Capacity of the JDMAI5 to discriminate between activity states and parent satisfaction/non satisfaction in the Prospective sample.

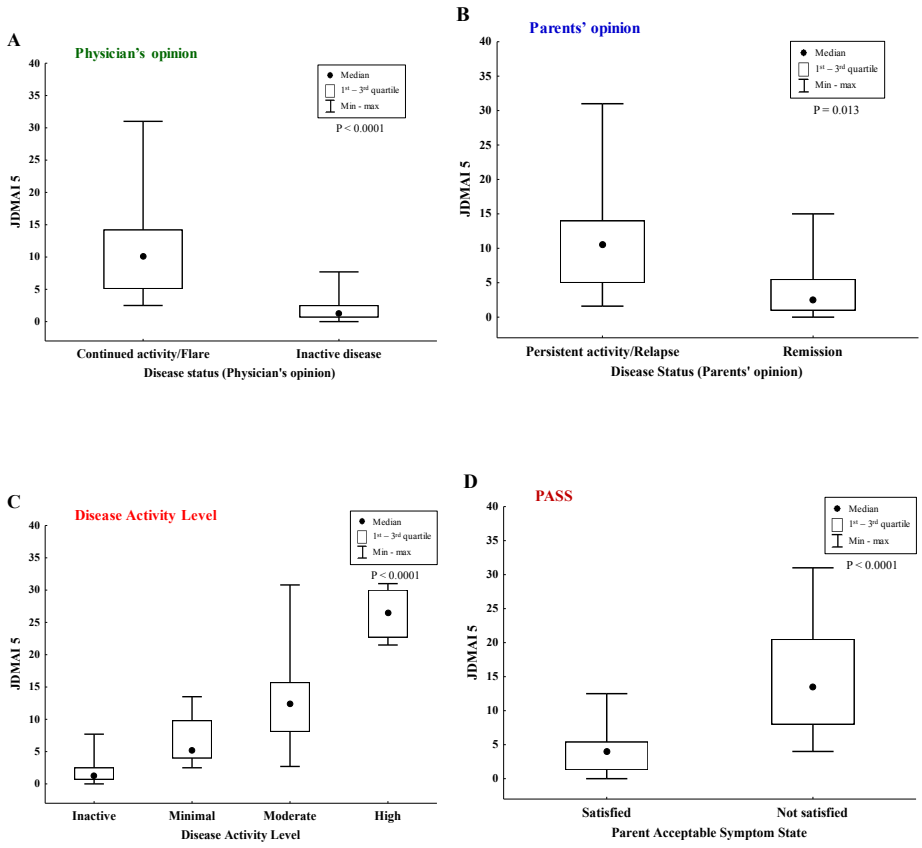
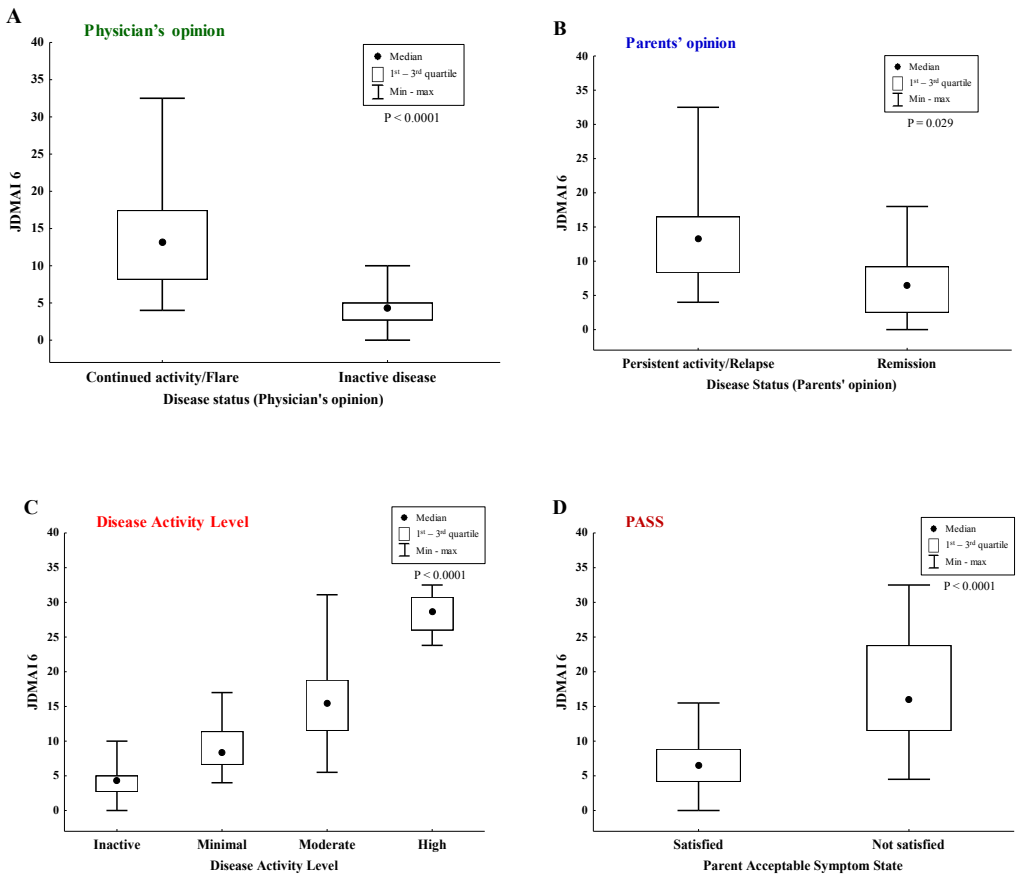


Figure A7. Capacity of the JDMAI6 to discriminate between activity states and parent satisfaction/non satisfaction in the Prospective sample.



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Health Questionnaire (CHQ), physician global damage, Myositis Damage Index (MDI), Quantitative Muscle Testing (QMT), Myositis Functional Index-2 (FI-2), Myositis Activities Profile (MAP), Inclusion Body Myositis Functional Rating Scale (IBMFRS), Cutaneous DermatomyositisDisease Area and Severity Index (CDASI), Cutaneous Assessment Tool (CAT), Dermatomyositis Skin Severity Index (DSSI), Skindex, and Dermatology Life Quality Index (DLQI).Arthritis Care Res (Hoboken) 2011;63:S118-57.

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