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ORIGINAL RESEARCH

Predictors of persistent active disease and the longitudinal development of organ damage, patient-reported outcomes and autoantibodies in long-term juvenile dermatomyositis

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ABSTRACT

Objective To quantify longitudinal development of disease activity, organ damage, patient-reported outcomes, and myositis autoantibody profiles in patients with juvenile dermatomyositis (JDM) after long-term follow-up, and to identify predictors for persistent active disease.

Methods Forty patients (65% female) diagnosed with JDM were clinically examined at two different time points (visits 1 and 2). We assessed clinically inactive/active disease by the updated PRINTO criteria and the Juvenile DermatoMyositis Activity Index (JDMAI). Organ damage was evaluated by Myositis Damage Index (MDI) and physical function by Childhood Health Assessment Questionnaire (CHAQ/HAQ). Myositis autoantibodies were measured by myositis line immunoassay.

Results Median disease duration from symptom onset was 15.1 (2.0–34.6) at visit 1 and 21.7 (7.6–42.7) years at visit 2. At visit 2, active disease (PRINTO) was found in 53%, impaired physical function (CHAQ/HAQ>0) in 40%, organ damage ($MDI_{total} \geq 1$) in 95% and myositis specific or associated antibodies in 33% of patients. Disease activity (JDMAI) was low in 24%, moderate in 8% and high in 3% of patients. There were no significant differences in organ damage and disease activity between visits. Higher disease activity and organ damage at visit 1 predicted persistent active disease at visit 2.

Conclusions After a median of 21.7 years from symptom onset, the majority of JDM patients still had active disease. Higher organ damage and disease activity at the initial visit predicted persistent active disease at follow-up. These results underscore the chronic nature of JDM, emphasising the need for enhanced early and long-term management strategies to improve patient outcomes.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Juvenile dermatomyositis (JDM) often results in persistent disease activity and organ damage, but longitudinal outcomes beyond 16 years were previously undocumented.

WHAT THIS STUDY ADDS

⇒ At a median of 21.7 years disease duration from symptom onset, 53% of patients had active disease and 95% had organ damage

⇒ Higher disease activity and damage after a median disease duration of 15.1 years were predictors of persistent disease between visits at 15.1 and 21.7 years.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings emphasise the need for enhanced early and long-term management strategies for JDM, and the predictors identified can guide intervention efforts to improve patient outcomes.

INTRODUCTION

Juvenile dermatomyositis (JDM) is a rare autoimmune disease of childhood, characterised by muscle weakness and characteristic skin lesions.[1] JDM is a systemic vasculopathy and can affect multiple organs.[1] Validated tools for assessing disease activity, organ damage and physical function in JDM have been developed and applied in a few clinical cross-sectional studies after 7–16 years of follow-up.[2–5] These studies show that most patients still experience active disease, organ damage and impaired physical function after long-term disease duration. However, there is no information about the longitudinal development of these key clinical outcomes after extended long-term follow-up.

A new tool to measure disease activity has recently been developed—the Juvenile DermatoMyositis Activity Index (JDMAI)—with validated cut-off values for low, moderate

and high disease activity.[6 7] Additionally, criteria for assessing clinical response have been established by the American College of Rheumatology (ACR)/EULAR.[8] However, none of these tools have been applied to longitudinal data from long-term follow-up studies.

Significant progress has been made in understanding myositis-specific autoantibodies (MSAs) and myositis-associated autoantibodies (MAAs) and their association to distinct clinical phenotypes in JDM.[9] However, whether their presence remains consistent over time is uncertain, and limited information exists regarding the long-term persistence of MSA's and MAA's in JDM patients after long-term follow-up.

In the NorJDM study, we have established a Norwegian retrospective inception cohort of patients with JDM. The cohort has been examined at two different time points, visit 1 (2005–2008) and visit 2 (2016–2018). The objective of the current study was to quantify the development of disease activity, organ damage, patient-reported outcomes, MSA and MAA profiles in JDM patients during long-term follow-up, and to identify predictors for persistent active disease.

METHODS

Patients and visits

In our longitudinal cohort study, we followed patients with JDM who had clinical examinations at two distinct time points within the same cohort.[4 5 10] Between September 2005 and June 2008, 60 JDM patients were examined as part of a comprehensive cross-sectional study conducted at Oslo University Hospital (visit 1). These patients were part of a retrospective inception cohort diagnosed with JDM in Norway from January 1970 to June 2006. Utilising the Norwegian population registry, we were able to track these patients and 95% of the identified, living patients participated in the study, as previously described in detail.[4] Importantly, patients were invited to participate regardless of their current follow-up status by paediatric or adult rheumatologists. A follow-up examination (visit 2) was performed between 2013 and 2016.[10] The current study reports data from JDM patients who participated in both visits 1 and 2. Disease duration was defined as time from onset of skin and/or muscle symptoms (as determined from the medical records) to visit 1 or 2.

The inclusion criteria were definite or probable dermatomyositis according to the Peter and Bohan criteria, diagnosis before the age of 18, and a minimum of 24 months from symptom onset to examination.

The study complies with the Declaration of Helsinki, and informed consents were obtained at both visits from all patients (if ≥16 years of age at time of visit), or parents (if <16 years of age at time of visit). The Regional Ethics Committee for Medical Research approved the study: S-05144, 2016/505 (for visit 1) and 2013/1039 (for visit 2).

Clinical measures at both visits

We clinically examined all included patients at visit 1 (by HS) and visit 2 (by KSB). Height and weight were measured, and body mass index (BMI) calculated.

Disease activity: disease activity was measured by Disease Activity Score (DAS) for JDM consisting of DAS skin (0–9) and DAS muscle (0–11); higher scores denote higher disease activity.[11] Also, the Myositis Disease Activity Assessment Tool (MDAAT), a combined tool consisting of the myositis disease activity assessment Visual Analogue Scale (MYOACT) and the Myositis Intention-to-Treat Activity Index (MITAX), was assessed.[12 13] Disease activity was also measured by the Physician Global Activity (PGA) (0–10).[14]

Organ damage: To assess organ damage, the Myositis Damage Index (MDI) was calculated, which defines damage in 11 domains (organ systems), with one to eight symptoms or signs (items) per domain.[15] The presence of organ damage was defined as MDI total score ≥1. At both visits, organ damage was assessed as clinically detectable damage present at the time of the visit (rather than cumulative organ damage that may have been present earlier but subsequently resolved).

Muscle strength and endurance: muscle strength was measured by the Manual Muscle Test (MMT-8) (0–80) and muscle endurance by the Childhood Myositis Assessment Scale (CMAS) (0–52).[16 17] We also used the newly developed hybrid MMT/Childhood Myositis Assessment Scale (hMC), which is composed of all eight items of the MMT-8 and three items of the CMAS: time of head lift, assessment of abdominal muscles and floor rise (0–100).[18] Higher score indicates better muscle strength.

Patient-reported outcomes measures (PROMs): to measure physical function, the Health Assessment Questionnaire (HAQ) was assessed in patients≥18 years, and the Childhood HAQ (CHAQ) in patients<18 years (range 0–3, where 0 indicates no difficulty with and three unable to perform daily activities).[19 20] The questionnaire was completed by patients and/or parents. Severely impaired physical function was defined as a CHAQ/HAQ score of ≥1.5. Also, Parent/Patient Global Assessment of overall well-being rated on a Visual Analogue Scale (VAS) ranging from 0 to 10 cm (0 no activity and 10 maximum activity). We used the Norwegian version of the Short-Form 36 health survey (SF-36) (0–100 scale), V.1.0, to assess health-related quality of life in patients ages≥14 years.[21] Lower scores indicate increased disability.

Disease activity states: clinically inactive disease was defined according to the modified PRINTO criteria; the presence of PGA≤0.2 and at least two of the three following: creatine kinase≤150 units/L, CMAS≥48 and MMT-8≥78.[22] By these criteria, patients were divided into clinically inactive and active disease. To categorise the varying degrees of disease activity, we utilised the JDMAI V.1,[6] which is a composite score consisting of PGA (0–10), Parent/Patient Global Assessment of overall well-being (0–10), hMC in deciles (0–10) and the VAS for skin activity (0–10). JDMDAI 1 cut-offs were defined as ≤2.4

Table 1 Patient and disease variables

	Visit 1 (n=40)	Visit 2 (n=40)	Change	P value
Female sex, n (%)	26 (65)	26 (65)		
Age, years	20.1 (6.7–48.9)	28.2 (13.7–58.4)	7.5	
Above 18 years	27 (68%)	36 (90%)	9	
Height (cm)	166±16	170±10	5	**0.03**
Weight (kg)	62 (23–115)	67 (44–112)	6.7	**<0.001**
BMI	21 (15–34)	23 (18–38)	1.8	**<0.001**
Disease duration, years	15.1 (2.0–34.6)	21.7 (7.6–42.7)	7.6	
DAS_{Total} (0–20↑)	4.5±2.7	4.5±2.5	0.1	0.94
$MYOACT_{Total}$ (0–70↑)	0.7 (0–6.3)	0.4 (0–4.9)	–0.1	0.20
$MITAX_{Total}$ (0–63↑)	3 (0–13)	3 (0–16)	0	0.06
MMT-8 (0–80↓)	79 (61–80)	78 (50–80)	–1	0.08
CMAS (0–52)	50 (28–52)	49 (31–52)	0	0.49
hMC (0–100↓)	92 (64–95)	90 (50–95)	1	0.13
PGA (0–10↑)	0.4 (0.4–2.5)	0.2 (0–3.2)	0.1	**0.03**
PGD (0–10↑)	0.6 (0–5.8)*	1.1 (0–4.9)	0.6	0.08
SF-36 PCS (0–100↓)	54.6 (32.4–61.5)†	53.7 (26.5–64.4)‡	0.1	0.40
CHAQ/HAQ (0–3↑)	0 (0–2)	0 (0–2)	0	0.70
CHAQ/HAQ>0 (n)	14 (35%)	16 (40%)	2	0.64
Inactive disease (n)	15 (38%)	19 (48%)	4	0.37
JDMAI	2.5 (0.5–9.5)	1.7 (0.5–12.3)	–0.2	0.20
On medication (n)§	12 (30%)	7 (18%)	5	0.13

Values are presented as mean (SD), median (range) or number (%).
↑, higher score denotes more activity/impairment/disability/damage; ↓, lower score denotes more activity/impairment/disability/damage.
Bold format, p<0.05
*n=33.
†n=35.
‡n=39.
§On medication, any use of immunosuppressive medication.
BMI, Body Mass Index; CHAQ/HAQ, Child/Adult Health Assessment Questionnaire; CMAS, muscle endurance by the Child Myositis Assessment Scale; DAS, Disease Activity Score; hMC, hybrid Muscle Manual Test/Childhood Myositis Assessment Scale; inactive disease, according to PRINTO criteria; JDMAI, Juvenile DermatoMyositis Activity Index score; MITAX, Myositis Intention to Treat Activity Index; MMT-8, total score for Manual Muscle Test; MYOACT, Myositis Disease Activity Assessment Visual Analogue scales; PGA, Physician Global Activity; PGD, Physician Global Damage; SF-36 PCS, Short-Form 36 Physical Component Summary.

for inactive disease, 2.5–6.6 low disease activity, 6.7–11 for moderate disease activity and >11 for high disease activity.[6] Patients with JDMAI, 1 cut-off ≥2.5, were defined to have active disease. Persistent active disease was defined as clinically active disease at both visits defined by PRINTO or JDMAI.

Clinical improvement: to define clinical response between visits 1 and 2, we used the 2016 ACR/EULAR Criteria for Minimal, Moderate and Major Clinical Response in JDM.[23] Clinical improvement was calculated using the outcome assessment calculator on the National Institutes of Environmental Health Sciences website based on the International Myositis Assessment and Clinical Studies Group (IMACS) core set measures.[24] IMACS improvement score was calculated using PGA and MMT-8 and at least two other IMACS core set measures (Patient/Parent Global Activity score, laboratory—muscle enzymes, extra muscular assessment—Myositis Disease Activity and functional assessment tools—CHAQ/HAQ, CMAS).

Medication

At the time of each visit, patients were categorised as being on or off immunosuppressive drugs, which was defined as glucocorticoids, synthetic disease-modifying antirheumatic drugs (sDMARDs) such as methotrexate, antimalarials, mycophenolate or biologic DMARDs.

Laboratory measurements

Serum samples were thawed and subjected to the following tests: (a) ANA screening by indirect immunofluorescence on HEp-2 cells at serum dilution 1:160. Only nuclear fluorescence patterns were considered positive. (b) Myositis line immunoassay A1 (EUROIMMUN AG, Lubeck, Germany) including the following recombinant

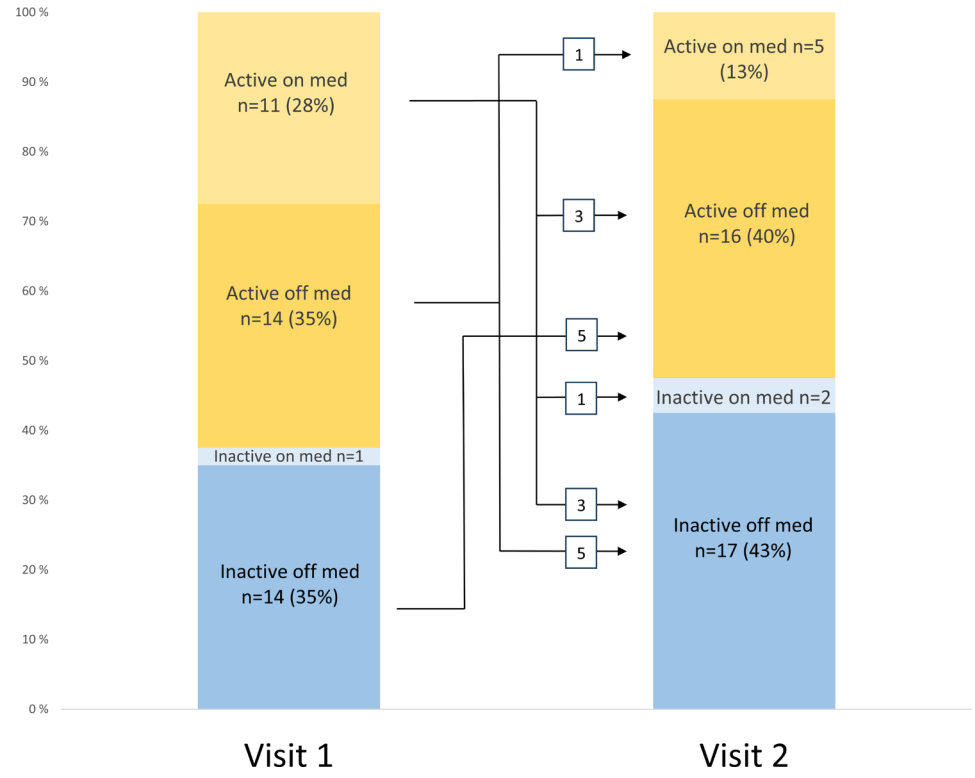

Figure 1 Change of disease activity category according to the updated PRINTO criteria and medication status from visit 1 to visit 2. Percentages are given according to the total cohort.

proteins: MDA5, TIF1-γ, NXP-2, SAE1, SAE2, HMGCR-S (Sigma), HMGCR-E (EUROIMMUN AG), Mup44. (c) The commercial myositis line immunoassay A2 (Myositis 3 Profile, EUROIMMUN AG) including the following MAA; Jo1, PL-7, PL-12, EJ, OJ, SRP, Mi-2, PM-Scl75, PM-Scl-100 Ku and Ro52. The immunoblot strips were scanned and evaluated digitally, using the Euroline scan. Signal intensities below 11 were regarded as negative. Muscle enzymes and inflammatory parameters (erythrocyte sedimentation rate and C-reactive protein) were measured by routine methods.

Statistical analysis

Continuous, normally distributed values are presented as mean and SD, while continuous, not normally distributed values are presented as median, with minimum and maximum ranges. Dichotomous values are presented as frequency (percentage). To compare variables between two visits, we used the paired sample t-test for continuous, normally distributed values and the Wilcoxon Signed Rank test for continuous, not normally distributed variables. McNemar's test was used to compare proportion of patients with specific characteristics between the visits, while Pearson's correlation analysis was used to explore disease outcomes. To determine predictors for persistent active disease, univariate logistic regression analyses were performed. The independent variables consisted of total disease activity or organ damage scores at visit 1, DAS_{total}, $MITAX_{total}$, $MYOACT_{total}$ and MDI_{total}. The strength of associations was expressed as ORs with 95% CIs. P-values<0.05 were considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics 24, 25 or 29.

RESULTS

Patient characteristics

Forty patients participated in both visits (visits 1 and 2) separated by a median of 7.5 (5.0–9.4) years. All patients fulfilled the 2017 EULAR/ACR classification criteria for idiopathic inflammatory myopathies and JDM, when applied retrospectively.[8] Their median age was 20.1 (6.7–48.9) years at visit 1 and 28.2 (13.7–58.4) years at visit 2 (table 1). Twenty-six patients (65%) were female (table 1). Median disease duration from symptom onset was 15.1 (2.0–34.6) at visit 1 and 21.7 (7.6–42.7) years at visit 2. Out of 13 children or adolescents<18 years of age at visit 1, nine became adults≥18 years old at visit 2.

Changes in disease variables between visit 1 and visit 2

Disease activity according to The PGA score decreased from visit 1 to visit 2, from 0.4 (0.4–2.5) to 0.2 (0–3.2) (p=0.03), while no significant differences between visit 1 and visit 2 were found at group level in disease activity measured by JDMAI, DAS and MYOACT, muscle strength (MMT-8) and muscle endurance (CMAS).

For PROMs, physical function (CHAQ/HAQ) and health-related quality of life (SF-36 PCS) were comparable between visits (table 1). Impaired physical function, indicated by a CHAQ/HAQ score of >0, was observed in 14 patients (35%) at visit 1 versus 16 (40%) at visit 2. At

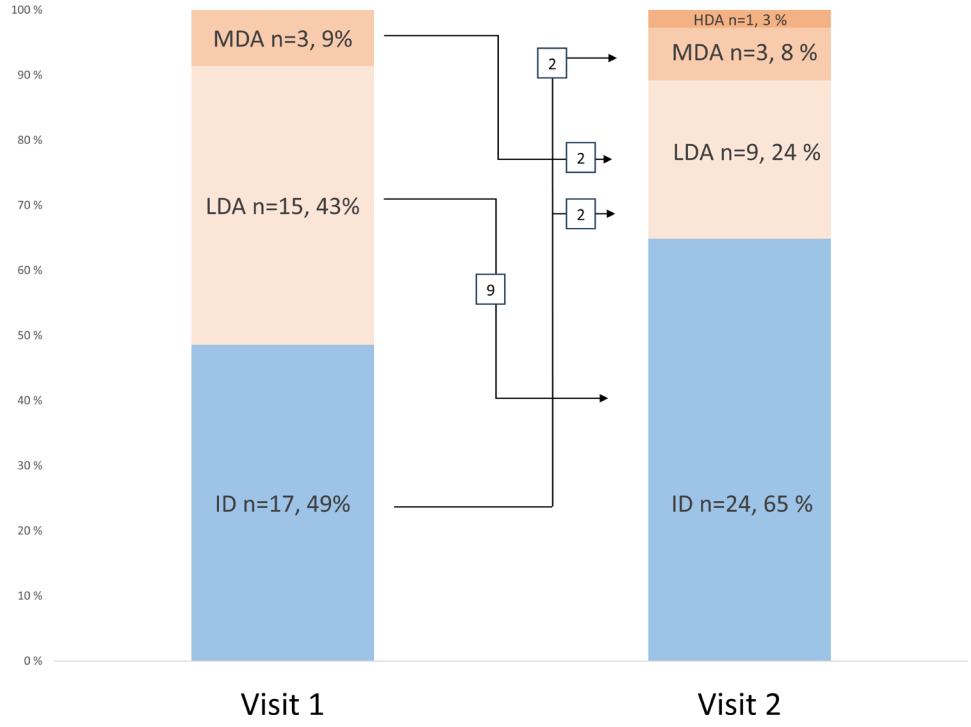

Figure 2 Change of disease activity category according to JDMAI from visit 1 to visit 2. Percentages are given according to the total cohort. HDA, high disease activity; JDMAI, Juvenile DermatoMyositis Activity Index; MDA, moderate disease activity; LDA, low disease activity; ID, inactive disease.

visit 2, only two patients (5%) reported severely impaired physical function (CHAQ/HAQ score ≥1.5).

Change of disease activity, medication category and clinical response between visits

When applying the updated PRINTO criteria, 25/40 (63%) of patients with clinically active disease at visit 1, 9 (36%) became inactive at visit 2, while 5/15 (33%) of patients with clinically inactive disease became active at visit 2 (figure 1). Notably, all five changed from inactive off-medication to active off-medication. At visit 2, of the 21 (53%) patients with clinically active disease, 5 (24%) were receiving immunosuppressive medication, while of the 19 patients with clinically inactive disease, 2 (11%) were on immunosuppressive medication. At visit 2, six patients (50%) who were on medication at visit 1 had discontinued their medication. Among the 28 patients who were off medication at visit 1, only one had begun immunosuppressive medication between visits (figure 1).

Three patients fulfilled the ACR/EULAR criteria for minimal clinical response between visit 1 and visit 2. All three patients had active disease at both visits based on updated PRINTO criteria. None of the patients fulfilled the ACR/EULAR criteria for moderate or major clinical response.

According to JDMAI, 17/35 (49%) patients had inactive disease at visit 1 compared with 24/37 (65%) at visit 2 (figure 2). Based on JDMAI, patients with low disease activity decreased from 15 (43%) to 9 (24%) at visit 2. Two patients with moderate disease activity at visit 1 converted to low disease activity at visit 2, and two patients with inactive disease converted to moderate disease activity (figure 2).

Evaluation of and changes in organ damage between visit 1 and visit 2

Damage in one or more organ systems (MDI total score≥1) was observed in 38 patients (95%) at visit 1 and 37 (95%) at visit 2. Median total MDI scores did not significantly differ between visit 1 and visit 2; 3 (0–9) versus 3 (0–6), respectively; p=0.33 (Table 2). At visit 2, the most prevalent affected organs with damage were muscle (74%), skeletal (51%) and skin (48%), with muscle weakness (69%), joint contracture (44%), skin calcinosis (32%) and cutaneous atrophy (31%). While muscle atrophy and cutaneous scarring decreased between visit 1 and visit 2; the number of patients with muscle weakness increased significantly from visit 1 to visit 2, n=17/40, 43% versus n=27/39, 68% (p=0.02).

Predictors of persistent active disease

At visit 2, the prevalence of persistent active disease was 16/40 patients (40%) based on the PRINTO criteria and 6/40 (15%) based on JDMAI criteria (low, moderate or high disease activity). We examined the predictors (measured at visit 1) of persistent active disease through univariate logistic regression analysis (table 3). When using persistent active disease by PRINTO criteria as outcome, we found an association with increased DAS_{total} (p=0.004), $MITAX_{total}$ (p=0.007) and $MYOACT_{total}$ (p=0.008) at visit 1. When using persistent active disease by JDMAI as outcome, we found an association with increased DAS_{total} (p=0.04), $MITAX_{total}$ (p=0.04)

Table 2 Organ damage by Myositis Disease Damage Index

	Visit 1 (n=40)	Visit 2 (n=39)	Change	P value
MDI_{total} (0–40↑)	3 (0–9)	3 (0–6)	0	0.33
Muscle damage	25 (63)	29 (74)	4	0.26
Muscle atrophy (clinical)	14 (35)	6 (15)	8	**0.045**
Muscle weakness	17 (43)	27 (69)	10	**0.02**
Skeletal damage	23 (58)	20 (51)	–3	0.58
Joint contracture	21 (53)	17 (44)	4	0.43
Osteoporosis	4 (10)	4 (10)	0	0.97
Vascular necrosis	1 (3)	0 (0)	–1	0.32
Cutaneous damage	31 (78)	19 (48)	–12	**0.02**
Calcinosis	17 (43)	12 (32)	–5	0.32
Alopecia	0 (0)	0 (0)	0	NA
Cutaneous scarring or atrophy	25 (63)	12 (31)	–13	**0.005**
Poikiloderma	1 (3)	1 (3)	0	0.99
Lipodystrophy	6 (15)	5 (13)	–1	0.78
Gastrointestinal damage	1 (3)	4 (10)	3	0.16
Dysphagia	1 (3)	3 (8)	2	0.29
Infarction of bowel	0 (0)	1 (3)	1	0.31
Pulmonary damage	6 (15)	5 (13)	–1	0.78
Dysphonia	1 (3)	1 (3)	0	0.49
Respiratory muscle damage	3 (8)	0 (0)	–3	0.08
Pulmonary fibrosis	2 (40)	4 (10)	2	0.39
Pulmonary hypertension	0 (0)	0 (0)	0	NA
Cardiovascular damage	1 (3)	3 (8)	2	0.29
Hypertension	1 (3)	3 (8)	2	0.29
Angina/coronary bypass*	0 (0)	1 (3)	1	0.38
Myocardial infarction*	0 (0)	1 (3)	1	0.38
Peripheral vascular damage	4 (10)	2 (5)	–2	0.41
Tissue or pulp loss	4 (10)	2 (5)	–2	0.70
Digit or limb loss or resection	1 (3)	1 (3)	0	0.99
Venous or arterial thrombosis	0 (0)	0 (0)	0	NA
Claudication*	0 (0)	0 (0)	0	NA
Endocrine damage	15 (38)	6 (15)	–9	0.20
Hirsutism or hypertrichosis†	9 (23)	3 (12)	–6	0.26
Irregular menses†	5 (24)	3 (17)	–2	0.58
Amenorrhea†	2 (10)	0 (0)	-2	0.16
Diabetes	0 (0)	0 (0)	0	NA
Ocular damage	0 (0)	0 (0)	0	NA
Cataract resulting in visual loss	0 (0)	0 (0)	0	NA
Visual loss, other	0 (0)	0 (0)	0	NA
Chronic infection	0 (0)	0 (0)	0	NA
Multiple infections	5 (13)	3 (8)	–2	0.48
Malignancy	0 (0)	1 (3)	1	0.30

Values are presented as median (range), or number (%) with score for the specific domain symptom/sign in each organ/system according to Myositis Disease Damage Index (MDI). ↑, higher score denotes more activity/impairment/disability/damage.
Bold format, p<0.05
*Evaluated only in patients aged ≥18 years, n=27 (visit 1) and n=36 (visit 2).
†Evaluated only in females after puberty, n=21 (visit 1) and n=26 (visit 2).
NA, not applicable.

Table 3 Predictors of persistent active disease according to JDMAI and PRINTO criteria

	JDMAI			PRINTO		
Independent variables at visit 1	OR	95% CI	P value	OR	95% CI	P value
DAS_{total}	1.50	1.01 to 2.16	**0.04**	2.37	1.32 to 4.24	**0.004**
$MITAX_{total}$	1.36	1.02 to 1.81	**0.04**	1.7	1.16 to 2.59	**0.007**
$MYOACT_{total}$	1.77	0.99 to 3.17	0.06	3.67	1.40 to 9.58	**0.008**
MDI_{total}	1.61	1.05 to 2.48	**0.03**	1.14	0.87 to 1.51	0.34

Persistent active disease at both visits, according to PRINTO criteria and JDMAI.
Bold format, p<0.05
DAS, Disease Activity Score; JDMAI, Juvenile DermatoMyositis Activity Index ; MDI, Myositis Damage Index; MITAX, Myositis Intention to Treat Activity Index; MYOACT, Myositis Disease Activity Assessment Visual Analogue scales; SF-36 PCS, Short-Form 36 Physical Component Summary.

and MDI_{total} (p=0.03) at visit 1. Due to high intercorrelation among predictors, multivariate analysis was not performed.

Myositis specific and myositis associated autoantibody profiles and clinical correlates

At visit 1, 7/40 patients (18%) were MSA positive, which included anti-NXP2 (n=1), anti-MDA5 (n=1), anti-TIF1-γ (n=1), anti-Mi2 (n=3) and anti-SRP (n=1). At visit 2, only 4 of 40 (10%) were MSA positive. The anti-NXP2 positive patient and anti-SRP positive patients at visit 1 remained positive, whereas both the anti-TIF1-γ and the anti-MDA5 positive patient became negative. Of the three anti-Mi2 positive patients at visit 1, two remained positive. The most common MAA at visit 2 was anti-PM75, 9 (23%). Anti-PM75 was found to correlate with both calcinosis (r_{sp}=0.41, p=0.01) and lipodystrophy (r_{sp}=0.38, p=0.02).

DISCUSSION

In our study, disease activity (DAS_{total}, $MITAX_{total}$ and $MYOACT_{total}$) and organ damage (MDI_{total}) at visit 1 predicted persistent active disease at visit 2. At visit 2, 53% of patients had active disease, 95% had signs of organ damage and 40% had impaired physical function after 21.7 years of disease duration. Muscle strength, muscle endurance and patient-reported outcomes remained stationary between the two visits separated by a median of 7.5 years. To the best of our knowledge, this is the first JDM study exploring the development of key clinical outcomes after long-term follow-up.

For the first time, both the JDMAI and modified PRINTO criteria have been used for assessment of disease activity in long-term JDM study. According to the PRINTO criteria, the proportion of patients with active disease was not statistically different between visits (60% and 53%). In comparison, the percentage of patients with disease activity based on the JDMAI (low, moderate or high) showed a decreasing trend from 51% to 33%. The PRINTO criteria seem to identify a higher number of patients with persistent or residual disease activity, suggesting its utility in capturing clinically significant, ongoing disease. On the other hand, the more pronounced reduction (although not significant) observed with the JDMAI indicates that it may be more sensitive to change. Our results indicate that using both tools together might provide a more comprehensive evaluation of disease activity in long-term follow-up settings, allowing for better-informed clinical decision-making.

We observed damage in one or more organ systems in 95% of JDM patients after a median of 21.8 years of follow-up. This is slightly higher compared with previous studies where MDI-based organ damage ranged between 60% and 90%.[2–4 25] In visit 2, prevalent manifestations of organ damage include muscle weakness, joint contracture, skin calcinosis and cutaneous atrophy. Although the median MDI score remained stable over time, there was a significant increase in MDI-scored muscle weakness from 43% to 69%.

In comparison, Ravelli *et al* found that 40% of their patients had reduced muscle strength after 7.7 years of disease duration.[2] Interestingly, in our study, the proportion of patients achieving maximum MMT8 score of 80 was 33% at visit 1 and 22% at visit 2. These findings may underscore the comprehensive and sensitive nature of the MDI in capturing overall organ damage, highlighting its utility in detecting subtle changes in disease status.

Our study identified potential predictors of persistent active JDM, defined as patients having clinically active disease at both visits. In univariable analyses, DAS_{total} and $MITAX_{total}$ measured at visit 1 (median 15 years after disease onset) were associated with persistent active JDM for both PRINTO-based and JDMAI-based assessments. Our findings align with the findings of Deakin *et al* who identified modified DAS for skin disease, from diagnosis to first-recorded visit, as a predictor of high skin disease activity.[26] Our results suggest that predictors of long-term disease activity may emerge later in the disease course, highlighting the cumulative burden of disease and its impact on ongoing activity.

Major MAAs and MSAs were similar between patients with active and inactive disease in our cohort. We have further observed that anti-PM75 was the most prevalent autoantibody, present in one of five MSA positive patients. Anti-PM75 autoantibodies are commonly found in systemic sclerosis patients and have been previously

linked to both myositis and calcinosis.[27] Interestingly, anti-PM75 in our cohort was associated with calcinosis and lipodystrophy at follow-up. Larger cohorts are needed to evaluate its value for early diagnosis and prognostics, particularly with regard to calcinosis.

Our study found that impaired physical function was present in 35% of patients at visit 1 and 40% at visit 2, though only 5% had severe disability (CHAQ/HAQ≥1.5) at visit 2.[2 28] This highlights the persistent functional limitations in a significant portion of JDM patients even long after disease onset, emphasising the importance of long-term monitoring and supportive interventions.

A major strength of our study is its foundation in a retrospective inception cohort. This design minimises bias towards more severe cases as patients were included regardless of whether they were still being followed by a paediatric or adult rheumatologist. Furthermore, we were able to apply a broad range of validated methods. However, some limitations apply: MDI and MMT-8 were scored by different examiners at visits 1 and 2, possibly allowing for scoring variability. Additionally, not all patients from visit 1 were able to participate in visit 2, possibly selecting for healthier patients and influencing the overall results and the statistical power of our findings. Furthermore, autoantibody status for MSA/MAA was evaluated by line blot assays, which are less sensitive compared with other advanced methods and not reliable in capturing TIF1γ-autoantibodies. Additionally, anti-PM75 was measured only at visit 2. Since only a few patients tested positive for MSAs, this limited our ability to assess the impact of MSA on long-term outcomes in JDM. Only medications used at the time of each visit were registered, potentially limiting our understanding of the relationship between medication use over time and the long-term development of disease activity.

Long-term outcome studies inherently reflect the treatment practices and standards of care at the time of JDM diagnosis. Our findings suggest that these early strategies were insufficient for patients diagnosed during our study period. This highlights the need for improved early intervention approaches and further research into long-term management strategies for JDM, especially considering that the long-term outcomes of patients treated with current early treatment strategies remain to be fully elucidated.

In conclusion, disease activity, organ damage, patient-reported outcomes and myositis autoantibody did not differ between the two visits at 15.1 and 21.7 years of disease duration. After a median disease duration of 21.7 years, 53% of JDM patients still had active disease, and organ damage remained prevalent. High disease activity and organ damage after 15.1 years was associated with persistent active JDM after 21.7 years, highlighting the need for enhanced early and long-term management strategies for JDM.

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