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# Autoantibodies and damage in patients with idiopathic inflammatory myopathies: A longitudinal multicenter study from the MYONET international network

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ABSTRACT

*Objective:* To study the trajectories of changes in damage over time and explore associations with autoantibody defined subgroups using a large international cohort of patients with idiopathic inflammatory myopathies (IIM).
*Methods:* Data from the MYONET registry, including patients who were tested for autoantibodies and had at least one assessment of damage using the Myositis Damage Index (MDI), were analyzed. Patients were sub-grouped according to their autoantibody profiles (myositis-specific, myositis-associated, or seronegative). The index date was defined as the time point for the first registered MDI assessment. The longitudinal trajectories of damage with autoantibody status as the main predictor were analyzed using linear mixed models.
*Results:* A total of 757 adult patients were included in this study. Each year of disease duration since diagnosis had an estimated MDI score increase of 0.16 units for the seronegative group (reference). Compared with the seronegative group as reference, patients with dermatomyositis-specific autoantibodies developed less damage per year of follow-up since diagnosis (average 0.08 less score, $P = 0.04$), whereas patients with anti-PM/Scl autoantibodies developed more damage per year of follow-up since diagnosis (average 0.28 higher score, $P =$

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0.03) independent of sex and age at diagnosis. The seronegative subgroup and the immune-mediated necrotizing myopathy autoantibody subgroup had the strongest correlation between severity of muscle damage and HAQ-DI scores at five years of follow-up, rho=0.84, $P < 0.001$ and rho=0.72, $P < 0.001$, respectively.
*Conclusion:* Our study is the first to describe patterns and trajectories of change in damage over time in relation to autoantibody defined subgroups in a large international multicenter cohort of patients with IIM. Patients with anti-PM/Scl scored a greater extent of damage, whereas patients with dermatomyositis-specific antibodies had less damage than seronegative patients. Severity in muscle damage had moderate to strong correlation with functional disability among the IMNM and seronegative subgroups with lower correlations for the other subgroups. These findings suggest that autoantibodies may be useful predictors of long-term damage.

## Introduction

Idiopathic inflammatory myopathies (IIMs) are rare systemic autoimmune diseases characterized by muscle inflammation and multiorgan involvement. Most patients with IIMs have myositis-specific autoantibodies (MSA) that are strongly associated with well-defined phenotypes, or myositis-associated autoantibodies (MAA), which may also be present in other diseases. For example, anti-Jo-1 autoantibodies are strongly associated with interstitial lung disease and arthritis, anti-Mi-2 autoantibodies associate with a high prevalence of skin lesions and a low frequency of cancer, and anti-PM/Scl autoantibodies with scleroderma-like skin lesions, dysphagia, and interstitial lung disease [1,2]. Furthermore, autoantibodies might have the potential to predict treatment response [3–5].

The involvement of skeletal muscle and/or extra-muscular manifestations may result in life-threatening diseases, such as rapidly progressive interstitial lung disease or malignancy, and can be associated with a high mortality rate (approximately10 % cumulative mortality during the first year after diagnosis), despite treatment with glucocorticoids, other immunosuppressive therapies, or immunomodulation [6]. Many patients who overcome this period have a high risk of developing disease-related damage; however, biomarkers that predict damage have not been studied in detail [7–9]. The International Myositis Assessment and Clinical Studies Group (IMACS) has defined disease damage as a persistent or permanent change in anatomy, physiology, and function, which develops from previously active disease, complications of therapy, or other events [10,11].

Limited information is available on the accumulated damage due to the scarcity of cohorts with long-term follow-up. Moreover, the potential effects of different autoantibodies on the level of damage are unknown. The MYONET registry (formerly EUROMYOSITIS) is an international consortium in which >20 participating centers worldwide have prospectively collected demographic, clinical, serological, and treatment data from patients with IIMs since 2003. To date, over 6500 patients have contributed to the registration, 4961 have longitudinal data, enabling identification of factors linked with relevant clinical outcomes. This international registry-based longitudinal study aimed to investigate the type and extent of damage accrued by patients with IIM according to autoantibody status, and to determine trajectories of accrued damage over time.

## Patients and methods

### Dataset

The longitudinal web-based international MYONET registry cohort (http://euromyositis.eu) was analyzed in this study. The entire dataset consisted of 4961 patients at the time of data export (February 1, 2021). Fourteen centers from 10 different countries contributed to the data (Table S1).

### Definitions

We excluded cases with no available antibody test results ($n = 2566$). Patients were then classified as definite (probability ≥90 %), probable (≥55 and <90 %), possible (≥50 and <55 %), or non-classifiable myositis (≤50 %) according to the European League Against Rheumatism / American College of Rheumatology (EULAR/ACR) classification criteria [12]. When available information, cases were subclassified into "dermatomyositis" (DM), "amyopathic dermatomyositis" (ADM), "polymyositis" (PM) or "inclusion body myositis" (IBM). Patients with juvenile DM were excluded. Patients with non-classifiable myositis and positive only for autoantibodies different from MSA or MAA (e.g., rheumatoid factor) ($n = 142$) were excluded. Patients with coexisting connective tissue disease (CTD) who fulfilled the relevant classification criteria were reclassified as having overlapping myositis (Fig. S1). Patients with DM, ADM, or PM who fulfilled the criteria for anti-synthetase syndrome (ASSD) or immune-mediated necrotizing myopathy (IMNM) were reclassified accordingly [13,14]. Myositis-associated cancer was defined as cancer within ± 3 years of IIM diagnosis. Pharmacological treatment was administered according to the local practice. Disease activity at index date was presented by using the six core set measures recommended by IMACS from patients with available information for each core set measure [15].

### Autoantibody defined subgroups of IIM

Patients were sub-grouped by the presence of autoantibodies as follows: 1) *ASSD* (anti-Jo-1, -PL-7, -PL-12, -EJ, -OJ), 2) *DM-specific autoantibodies* (anti-MDA5, -TIF1γ, -Mi-2, -SAE, -NXP2), 3) *IMNM-autoantibodies* (anti-SRP, -HMGCR), 4), *MSA- and MAA+* (anti-Ro-52, -U1RNP, -Ku), 5) *PM/Scl*, and 6) negative to any (*seronegative*). The assay used for testing autoantibodies was dependent on local practice. Of the 757 cases, 258 (34 %), 161 (21 %), 70 (9 %), and 14 (2 %) were determined by immunoprecipitation, line blotting, ELISA and other methods, respectively. The method was unknown in 254 (34 %) cases (Table S2).

### Myositis damage index

The MDI scores were obtained from the MYONET registry. The extent score consists of 11 domains that evaluates damage in different organs including muscular, skeletal, cutaneous, gastrointestinal, pulmonary, cardiovascular, peripheral vascular, endocrine, ocular, infection, and malignancy [10,16]. Each organ domain consists of two to eight items scored as present or absent. An item must be observed for the first time after the diagnosis and the first possible time-point to score damage is six months after diagnosis. Damage manifestations do not need to be attributed to the myositis disease. The presence or absence of each item is summarized as the total extent of the damage score (potential score of 0 – 38), where zero indicates no damage. The MDI also has a severity score where each organ domain has a 10-cm VAS to measure the severity of damage (MYODAM). The VAS scores of MYODAM are summarized as the total severity of damage score (potential score 0 −110) where zero indicates no damage.

### Early and late damage

The index date was defined as the time point for the first registered

MDI assessment. The development of damage is considered as a slow process, and accruing organ damage may not be detectable within 1 or 2 years [17]. The MDI extent scores at the index date and at five years after the first MDI assessment were used to describe early and late damage, respectively. The ten most frequently scored individual MDI items were determined at each time point based on all available MDI data.

### *Statistical analysis*

Means (standard deviation, SD) and medians (interquartile range, IQR) were calculated from the demographic characteristics of patients at the index date. Statistical differences between groups in terms of continuous data were analyzed using *t*-tests, and in terms of proportions, using $X^2$ tests. To investigate the clinical relevance of the accrued damage over time, Spearman's correlation analyses between MDI severity score (overall and muscle domains) and the Health Assessment Questionnaire (HAQ-DI) were conducted.

The trajectory on the change in the MDI extent score over the course of follow-up as a function of the autoantibody group was tested using a linear mixed-effects regression model for repeated measurements. A within-patient correlation was included in the models to adjust for the clustered variation in each patient (each patient was fitted to a random effect). Finally, an interaction term (autoantibody group – years of follow-up since diagnosis) was included to determine whether the impact of time on damage accrual differed between the autoantibody groups. We chose to include all available data points from the registry and handle missing data by using a mixed-effect regression model. This model is suitable for analyzing registry data where data is missing at random because the model includes all values in the estimation sample [18]. Statistical significance was set at $P < 0.05$. All analyses were performed using the R software version 4.1.2 [19].

**Table 1**
Demographic characteristics accumulated clinical manifestations, and disease activity at index date of 757 patients from the MYONET registry with at least one Myositis Damage Index assessment and one available autoantibody test.

| | ASSD $n = 214$ | DM-assoc. $n = 122$ | IMNM $n = 46$ | MAAs $n = 83$ | PM/Scl $n = 58$ | None $n = 234$ | Total $n = 757$ |
|---|---|---|---|---|---|---|---|
| Women, n (%) | 150/213 (70) | 73/121 (60) | 32/45 (71) | 58/81 (72) | 42 (72) | 158/231 (68) | 513/749 (69) |
| Mean age (SD) at diagnosis (years), ($n = 725$) | 50 (14) | 49 (18) | 53 (15) | 50 (14) | 49 (18) | 52 (16) | 52 (16) |
| Disease duration at index date (years), ($n = 738$), median (IQR) | 1.5 (0.5, 4.2) | 1.4 (0.3, 4.15) | 2.3 (0.7, 6.9) | 1.9 (0.8, 6.1) | 1.5 (0.8, 4.8) | 1.8 (0.6, 5.0) | 1.62 (0.5, 4.9) |
| Diagnosis according to EULAR/ACR criteria, n (%) | | | | | | | |
| Polymyositis | – | 14 | 1 | 21 | 15 | 63 | 114 (15) |
| Dermatomyositis | – | 96 | – | 15 | 19 | 118 | 248 (33) |
| Amyopathic dermatomyositis | – | 7 | – | 1 | | 3 | 11 (1) |
| Overlap with a CTD myositis | – | 4 | – | 39 | 22 | 16 | 81 (10) |
| Inclusion body myositis | – | 1 | – | 7 | 2 | 27 | 37 (5) |
| Antisynthetase syndrome | 214 | – | – | – | – | – | 214 (28) |
| Immune-mediated necrotizing myopathy | – | – | 45 | – | – | 7 | 52 (7) |
| Clinical features at any point of follow-up, n (%) | | | | | | | |
| Dysphagia | 56/190 (29)*** | 47/105 (45) | 21/42 (50) | 43/72 (60) | 26/52 (50) | 144/225 (64)*** | 337/686 (49) |
| Interstitial lung disease | 159/206 (77)*** | 29/106 (25)*** | 9/42 (21)** | 26/75 (34) | 25/56 (45) | 52/216 (24)*** | 300/701 (43) |
| Heart involvement | 25/180 (14) | 7/99 (7) | 7/38 (18) | 9/64 (14) | 3/48 (6) | 36/205 (18) | 87/634 (14) |
| Raynaud's phenomenon | 86/191 (45)*** | 17/97 (18)** | 10/42 (24) | 30/73 (41) | 21/52 (40) | 58/215 (27)* | 222/670 (33) |
| Arthritis | 109/204 (53)*** | 19/107 (18)** | 4/44 (9)** | 26/79 (33) | 17/54 (32) | 42/226 (19)** | 217/714 (30) |
| Myositis- associated cancer[a] n (%) | 9/20 (45) | 20/27 (74)*** | 0/6 (0)* | 4/8 (50) | 1/4 (25) | 14/38 (37) | 48/107 (44) |
| Ethnicity ($n = 737$), n (%) | | | | | | | |
| Caucasian | 193 (93)* | 97 (81)*** | 33 (77)* | 75 (92) | 50 (86) | 212 (93)* | 660 (90) |
| Other | 14 (7) | 23 (19) | 10 (23) | 7 (8) | 8 (14) | 15 (7) | 77 (10) |
| Time of follow-up (years), median (IQR) | 4.4 (1.8, 9.3) | 4.8 (1.6,9.9) | 7.7 (3.0,13.8) | 4.8 (2.1,8.4) | 4.6 (1.6,9.8) | 4.6 (1.9,9.1) | 4.7 (1.9,9.5) |
| Disease Activity Core set measures, median (IQR) | | | | | | | |
| Physician global assessment VAS (0–100), ($n = 639$) | 15 (5, 31) | 14 (4, 39) | 20 (8, 46) | 16 (6, 25) | 12 (6.5, 23) | 16 (6, 40) | 15 (6, 34) |
| Patient global assessment VAS (0–100), ($n = 597$) | 39 (15.5, 55) | 25 (10, 61)* | 50.5 (18.5, 73) | 40 (20, 59.5) | 36.5 (13, 68.8) | 50 (22, 67.8)** | 42 (16, 62) |
| MMT-8 (0 - 80), ($n = 596$) | 77 (71, 80)*** | 76 (69, 80)* | 69.5 (55, 78) | 75 (70, 79) | 73.5 (60, 80) | 69 (59, 75)*** | 74 (65, 79) |
| HAQ-DI, (0 – 3), ($n = 585$) | 0.6 (0.1, 1.1)** | 0.5 (0, 1.3)* | 0.9 (0.3, 1.4) | 0.9 (0.1, 1.5) | 0.75 (0.3, 1.4) | 1.0 (0.4, 1.6)*** | 0.75 (0.1, 1.4) |
| Creatine kinase (as ratio of ULN), ($n = 514$) | 0.53 (0.3, 1.9)* | 0.43 (0.3, 1.6)** | 1.42 (0.6, 3.1)*** | 0.66 (0.35, 1.88) | 0.67 (0.25, 1.8) | 0.9 (0.4, 2.8)*** | 0.6 (0.4, 2.1) |
| Extramuscular activity VAS (0–100), ($n = 658$) | 10 (0.75, 24.3) | 11.5 (1.3, 27.8) | 7 (0, 20.5) | 10 (0, 20.3) | 8.5 (0, 17) | 8 (0, 19.3) | 10 (0, 21) |
| MYOACT score, (0 – 60), ($n = 637$) | 2.7 (1.0, 6.5) | 2.5 (1.0, 6.5) | 2.3 (1.0, 7.4) | 2.9 (1.0, 6.5) | 2.7 (0.5, 6.1) | 3.3 (1.3, 7.6) | 2.9 (1.1, 6.8) |
| MDI extent of damage, median (IQR) | 3 (2, 6) | 2 (1, 4)*** | 3 (1, 5) | 3 (2, 5) | 4 (2, 6)*** | 3 (2, 6) | 3 (1,5) |

* <0.05,.
** <0.01,.
*** <0.001

Chi-square or Fisher's exact tests were used to compare each autoantibody group with the rest.

[a] Malignancy diagnosed within 3 years3 years of the idiopathic inflammatory myositis diagnosis. The denominator stands for the available number of patients with information on cancer.

‡ MMT-8, manual muscle test-8 score; HAQ-DI, Health Assessment Questionnaire-Disability index; VAS, visual analog scale; ULN, upper limit of normal; MYOACT, myositis disease activity assessment tool; CTD: connective tissue disease. DM: dermatomyositis; IMNM: immune-mediated necrotizing myopathy; ASSD: antisynthetase syndrome autoantibodies; MAA: myositis-associated autoantibodies.

*Ethical approval*

This study was approved by the Regional Ethics Committee in Stockholm, Sweden (Dnr. 2008/1919–31/3; Dnr. 2009/1934–32; Dnr. 2013/1390–32; Dnr. 2017/922–32; Dnr. 2019–01,593; Dnr. 2023/00,244–02). Ethical approval is required for each centre where the registry is implemented and informed consent is obtained from all included patients. For this study each participating center obtained local ethical approval.

## Results

*Study population*

Of the reclassified 1828 patients, 757 met the criteria for IIM and were included (Table S1). The demographic and clinical features of the patients at index date are presented in Table 1. Seventy percent of the patients were women, with a mean age at diagnosis of 52 years. The two most frequent clinical phenotypes were DM (33 %) and ASSD (28 %). The most frequent autoantibodies were anti-Jo-1 (22 %, $n = 174$), -PM/Scl (8 %, $n = 58$), -Mi-2 (6 %, $n = 44$), -TIF1γ (6 %, $n = 41$), and -SRP (4 %, $n = 33$). The median time from diagnosis to index date was 1.6 years (IQR 0.5 – 4.9).

*Extent of damage*

At the index date, the overall median MDI score was 3 [1–5], and 85 % of the patients had at least one registered damage item. The frequency of the MDI scores per organ/system on the index date is presented in Table 2. At the index date, the three most frequent organs/systems with any damage were the skeletal muscle (66 %), lungs (33 %), and gastrointestinal tract (23 %). Arterial hypertension, dysphonia, sexual dysfunction, cutaneous scarring, and impaired lung function were among the 10 most frequent items within all the domains. At five years of follow-up, the overall MDI extent of damage was 4 [2–6]. Regarding the most frequent items of damage all three muscle items (muscle atrophy, muscle dysfunction, and muscle weakness not attributable to active disease), lung fibrosis, dysphagia, arterial hypertension, sexual dysfunction, cataracts, osteoporosis with fracture, and irregular menses were the 10 most frequent (Fig. 1).

*Autoantibodies and damage*

At the index date, patients with DM-specific autoantibodies had the lowest MDI extent score, compared to the rest of the subgroups, whereas the anti-PM/Scl subgroup had the highest MDI extent score compared to the rest of the subgroups, (Table 1). The ASSD subgroup had higher frequency of lung fibrosis and lower frequency of persistent muscle weakness, muscle dysfunction, or muscle atrophy as well as dysphagia than the other groups. The seronegative subgroup had higher frequency of muscle atrophy, muscle dysfunction or dysphagia and lower frequency of lung fibrosis than the other subgroups. After excluding patients with IBM at index date, we found that the frequency of dysphagia was still significantly higher in seronegative patients compared with the other subgroups. The IMNM subgroup had higher frequency of persistent muscle weakness than other groups ($P = 0.02$). Dysphonia was more frequent among the seronegative subgroup than among other groups ($P = 0.04$) (Fig. 2).

At the five-year follow-up, the overall MDI extent score was comparable between all the subgroups. There were, however, notable differences in specific items of damage. For instance, the DM-specific autoantibody subgroup had lower frequency of persistent muscle weakness than the other groups ($P = 0.01$). The ASSD subgroup had higher frequency of lung fibrosis and lower frequency of dysphagia than the other groups. The seronegative subgroup had higher frequency of muscle atrophy and dysphagia than the other subgroups. No differences

**Table 2**
Organ damage and specific damage in 757 patients at first Myositis Damage Index assessment (index date).

| Organ systems in MDI | |
|---|---|
| Muscle severity, VAS, mean, (SD) | 1.4 (1.7) |
| Muscle damage[a], n (%) | 505 (66) |
| Muscle dysfunction | **352/696 (51)** |
| Muscle weakness not attributable to active disease | **351/750 (48)** |
| Muscle atrophy | **242/753 (32)** |
| Pulmonary severity, VAS, mean, (SD) | 0.8 (1.5) |
| Pulmonary damage, n (%) | 250/750 (33) |
| Lung fibrosis | **199/740 (27)** |
| Dysphonia | **58/741 (8)** |
| Impaired lung function | **52/738 (7)** |
| Pulmonary hypertension | 28/715 (4) |
| Gastrointestinal severity, VAS, mean, (SD) | 0.3 (1.0) |
| Gastrointestinal damage, n (%) | 170/754 (23) |
| Dysphagia | **155/752 (21)** |
| Gastrointestinal dysmotility | 30/751 (4) |
| Gastrointestinal infarction | 3/740 (0.4) |
| Cardiovascular severity, VAS, mean, (SD) | 0.2 (0.8) |
| Cardiovascular damage, n (%) | 115 (15.1) |
| Hypertension | **99/747 (13)** |
| Ventricular dysfunction | 20/745 (3) |
| Myocardial infarction | 17/739 (2) |
| Angina | 10/717 (1) |
| Cutaneous severity, VAS, mean, (SD) | 0.3 (0.8) |
| Cutaneous damage, n (%) | 115/751 (15) |
| Calcinosis | 26/706 (4) |
| Alopecia | 55/747 (7) |
| Cutaneous scarring or atrophy | **56/747 (8)** |
| Poikiloderma | 19/747 (3) |
| Lipodystrophy | 8/743 (1) |
| Endocrine severity, VAS, mean, (SD) | 0.3 (0.7) |
| Endocrine damage, n (%) | 150/729 (21) |
| Diabetes mellitus | 51/712 (7) |
| Hirsutism | 20/692 (3) |
| Amenorrhea | 34/613 (6) |
| Irregular menses | 38/607 (6) |
| Infertility | 27/609 (4) |
| Sexual dysfunction | **61/610 (10)** |
| Growth failure[b] | NA |
| Delay in secondary sexual characteristics[b] | NA |
| Skeletal severity, VAS, mean, (SD) | 0.4 (1.1) |
| Skeletal damage, n (%) | 93/753 (12) |
| Joint contracture | 36/751 (5) |
| Osteoporosis with fracture | 41/736 (6) |
| Avascular necrosis | 5/743 (1) |
| Deforming arthropathy | 28/736 (4) |
| Ocular severity, VAS, mean, (SD) | 0.2 (1.0) |
| Ocular damage, n (%) | 61/739 (8) |
| Cataract | 54/738 (7) |
| Vision loss | 15/735 (2) |
| Infection severity, VAS, mean, (SD) | 0.1 (0.6) |
| Infection, n (%) | 40/689 (6) |
| Chronic infection | 22/681 (3) |
| Multiple infections | 20/685 (3) |
| Malignancy severity, VAS, mean, (SD) | 0.3 (1.1) |
| Malignancy, n (%) | 38/727 (5) |
| Peripheral vascular severity, VAS, mean, (SD) | 0.05 (0.3) |
| Peripheral vascular damage, n (%) | 29/752 (4) |
| Tissue pulp loss | 11/751 (2) |
| Digit loss | 2/750 (0.3) |
| Thrombosis | 18/749 (2) |
| Claudication | 4/733 (0.5) |
| MDI score > 1 | 647 (85) |
| Severity of damage (MYODAM) | 4.1 (4.7) |

[a] The presence of at least one item in each organ system category was recorded to describe the frequency of damage by each domain.

The ten most frequent damage items are in highlighted text.

VAS, visual analogue scale (0–10); MDI, myositis damage index; MYODAM, myositis damage score.

[b] Not assessed as JDM patients were excluded.

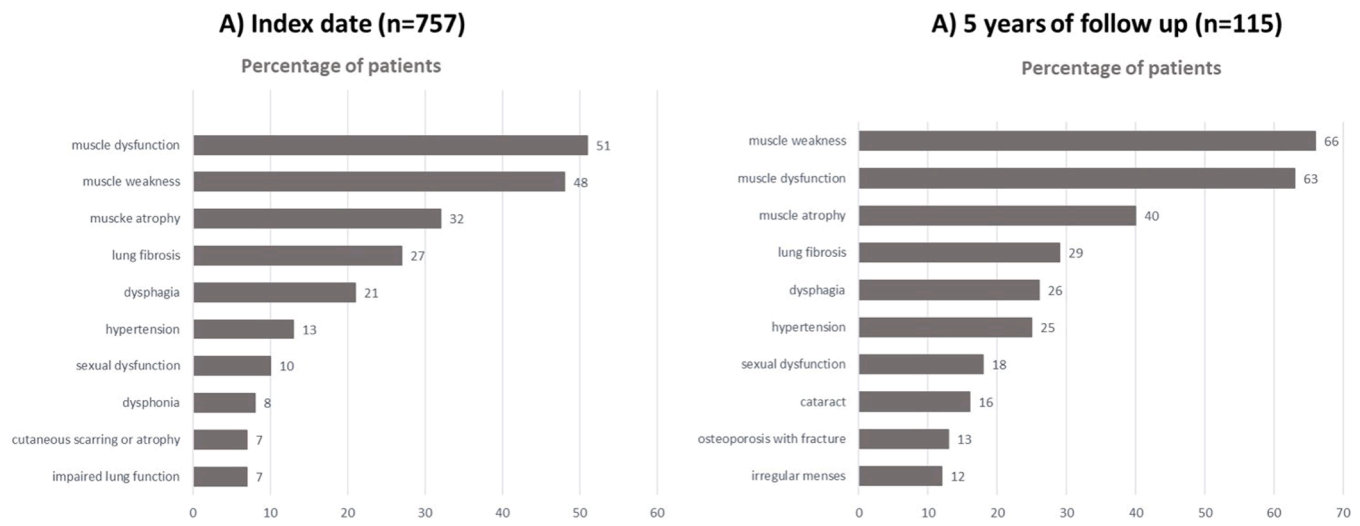


**Fig. 1.** Frequency of the 10 most common Myositis Damage Index (MDI) at index date and after 5 years of follow up.

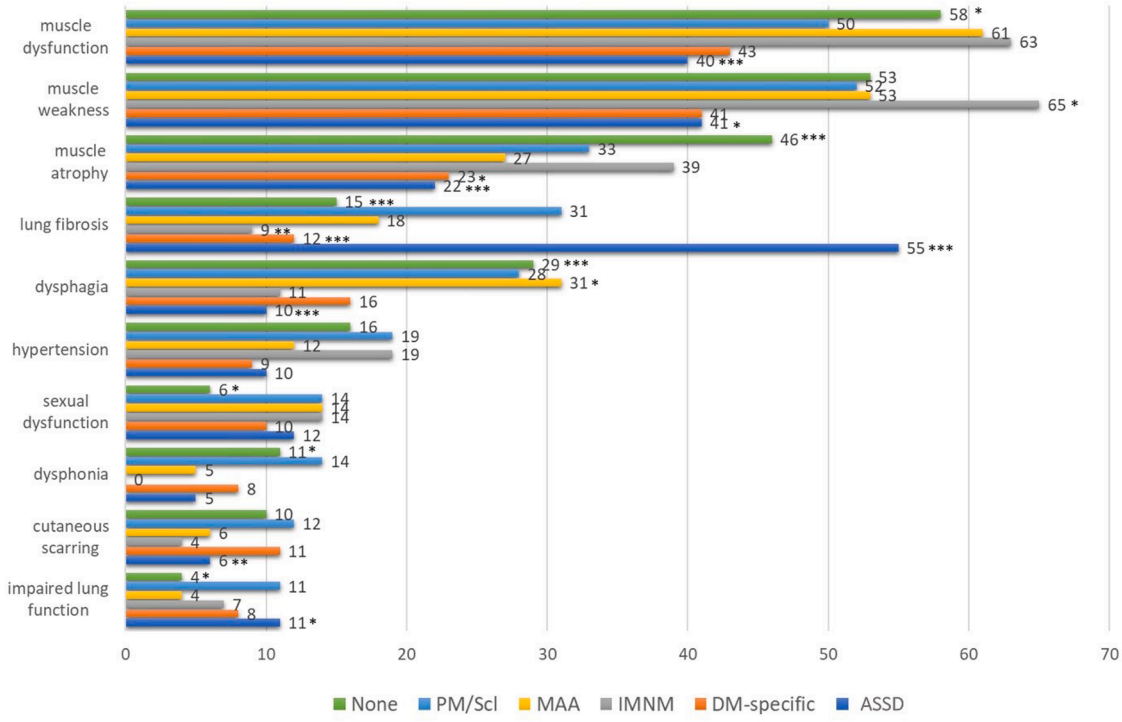


**Fig. 2.** Frequency of the 10 most common items of Myositis Damage Index extent score by autoantibody-defined subgroups at index date ($n = 757$).
Legend: The numbers represent percentages. *<0.05, **<0.01, ***<0.001. Chi-squared or Fisher's exact tests were used to compare each autoantibody-defined subgroup with the rest. MAA: myositis associated autoantibodies, IMNM: immune-mediated necrotizing myopathies, DM-specific: dermatomyositis specific autoantibodies, ASSD: Antisynthetase syndrome.

were found in the remaining most frequent items (Fig. 3).

*Correlation between severity of muscle damage and physical disability*

We found a weak but significant correlation between the overall MYODAM and HAQ-DI at the index date (rho=0.36, $P < 0.001$), which became moderate at five-year follow-up (rho=0.61, $P < 0.001$). As not all patients may have developed extra-muscular damage, we analyzed only the muscle domain of MYODAM and found a moderate-strong correlation with the HAQ-DI score (rho=0.42 at index; rho=0.72 at five-year follow-up, $P < 0.001$ for both). Furthermore, a correlation analysis between severity of damage and HAQ-DI by each autoantibody-defined group showed that the seronegative group and the IMNM group had the strongest correlation with HAQ-DI scores at five years of follow-up (rho=0.84, $P < 0.001$ and rho=0.72, $P < 0.001$, respectively) (Table S3).

*Change of damage over time*

Data on individual MDI items from the index date to five years were available for 115 patients. Cataracts were more frequent at five years follow-up compared with the index date (6% vs. 16 %, $P = 0.04$), whereas impaired lung function tended to be less frequent (6% vs. 1 %, $P = 0.06$) (Table 3). No significant changes were found on the other items.

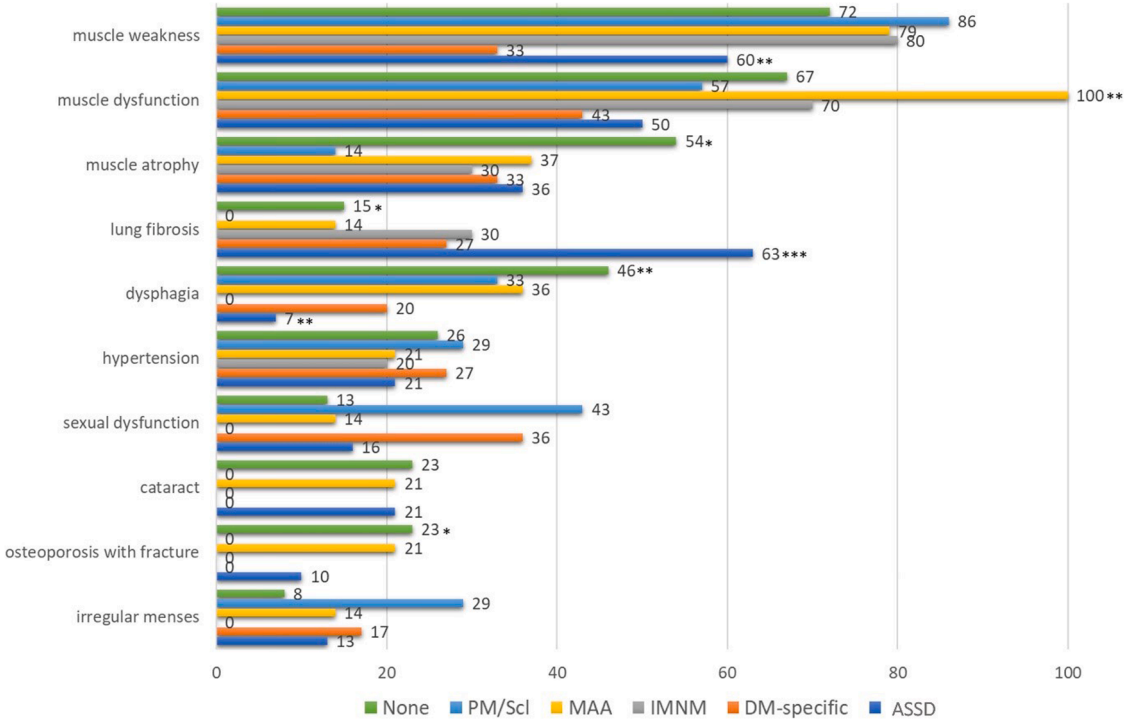


**Fig. 3.** Frequency of the 10 most common items of Myositis Damage Index extent score by autoantibody-defined subgroups at 5 years follow up ($n = 115$).
Legend: The numbers represent percentages. *<0.05, **<0.01, ***<0.001. Chi-squared or Fisher's exact tests were used to compare each autoantibody group with the rest. MAA: myositis associated autoantibodies, IMNM: immune-mediated necrotizing myopathies, DM-specific: dermatomyositis specific autoantibodies, ASSD: Antisynthetase syndrome.

To examine the change in the MDI extent score over time, we used a linear mixed-effects regression model for repeated measurements (Table 4). For the seronegative subgroup (reference) we estimated an increase of 0.16 units in the MDI extent score per year since diagnosis. Compared with the reference subgroup, the DM-specific autoantibody subgroup registered a lower change in the MDI extent score per unit of time (i.e., each year of follow-up) over the entire follow-up period (on average 0.08 units per year since diagnosis), while the anti-PM/Scl subgroup registered a higher change in the MDI extent score per unit of time (i.e., each year of follow-up) over the entire follow-up period (on average 0.28 units per year since diagnosis), independent of sex and age at diagnosis (Fig. 4). The subgroup with myositis-associated autoantibodies registered a lower change in the MDI extent score over the follow-up period than the seronegative subgroup; however, this significance did not persist after sensitivity analyses. We fitted two additional models for sensitivity analyses. First, a model restricted to a follow-up period less than five years showed similar results for the DM-specific autoantibody subgroup but not for the anti-PM/Scl autoantibody subgroup, suggesting a later development of damage by longer follow-up (> five years after diagnosis) for the latter subgroup. Lastly, we fitted a model excluding patients with IBM (sensitivity model 2), as they tend to be older at diagnosis, often develop muscle atrophy early, and are frequently seronegative, showing similar results in the trajectories of MDI extent score (Table S4). Sensitivity model 3 and 4 were restricted to a period of >5 and > 10 years, respectively, to ensure that type I error was minimized (Table S5). We did not find a difference in the developing of damage between the autoantibody-defined groups This suggests that after 5 years of follow-up the accrual organ damage as measured by the MDI extent score may not be attributed only by the autoantibody status, rather mainly due to ageing and possibly by other non-measured confounding variables such as side effects of pharmacological treatment. Lastly, sensitivity analysis 6 included a dichotomous variable for center (Sweden vs. other countries) and the trajectories of MDI extent during follow-up remained unchanged (Table S6).

## Discussion

Herein, we describe the patterns and trajectory of damage over time in a large international cohort of patients with IIMs, including the effect of autoantibodies. Our study sample represents the entire spectrum of patients with myositis, including patients from several countries on two continents, and covers a large variety of clinical and immunological manifestations.

Damage to the muscular, pulmonary, and gastrointestinal systems was most frequently recorded in our cohort. A similar distribution of damage extent was reported in a single-center cohort of 96 adult patients with IIMs from the National Institute of Health (NIH) [17]. In our study, however, we observed notable differences between autoantibody-defined subgroups in the pattern of damage. For example, at the first damage assessment, the ASSD subgroup had a lower frequency of muscle atrophy and persistent muscle weakness than the other groups. The DM-specific autoantibodies subgroup and the IMNM subgroup had lower prevalence of lung fibrosis than the other groups, whereas the ASSD subgroup was highly associated with this damage. In addition, chronic dysphagia was less common in the ASSD subgroup than in the other groups at both the index date and at five years of follow-up. Another relevant example of the difference between the autoantibody-defined subgroups was that the DM-specific autoantibody subgroup had the lowest score of damage at the index date compared to the other groups. Among the DM-specific autoantibodies subgroup, anti-Mi-2 autoantibodies seem to confer a lower risk of remaining on treatment over time, even though they are often associated with severe inflammatory infiltrates in muscle biopsies [20]. Anti-MDA5 autoantibodies have been reported to be associated with less perifascicular atrophy, few or no perivascular inflammatory infiltrates in muscle biopsies, and a lower degree of upregulated interferon signature compared to non-anti-MDA5 muscle biopsies [21–23]. These observations may explain the minimal clinical muscle involvement and good response to pharmacological treatment, which explains why the

**Table 3**
Frequency of each damage domain* and individual items at index date and at 5 years of follow-up among patients with data at both assessments ($n = 115$).

| | Index date n (%) | 5 years n (%) |
|---|---|---|
| Muscular damage | 87/115 (76) | 89/115 (77) |
| Muscle atrophy | 44/115 (38) | 46/115 (40) |
| Muscle weakness | 73/114 (64) | 76/115 (66) |
| Muscle dysfunction | 62/106 (59) | 72/114 (63) |
| Skeletal damage | 20/113 (18) | 30/114 (26) |
| Joint contracture | 6/113 (5) | 8/114 (7) |
| Osteoporosis with fracture | 7/112 (6) | 15/114 (13) |
| Avascular necrosis | 2/112 (2) | 9/114 (8) |
| Deforming arthropathy | 8/107 (8) | 11/114 (10) |
| Cutaneous damage | 20/115 (17) | 18/115 (16) |
| Calcinosis | 6/114 (5) | 7/115 (6) |
| Alopecia | 8/115 (7) | 7/117 (6) |
| Cutaneous scarring or atrophy | 10/114 (9) | 10/115 (9) |
| Poikiloderma | 1/114 (1) | 2/115 (2) |
| Lipodystrophy | 0/114 (0) | 0/115 (0) |
| Gastrointestinal damage | 38/114 (33) | 34/114 (30) |
| Dysphagia | 36/114 (32) | 30/114 (26) |
| Gastrointestinal dysmotility | 5/113 (4) | 8/114 (7) |
| Gastrointestinal infarction | 1/110 (1) | 1/114 (1) |
| Pulmonary damage | 42/113 (37) | 41/115 (36) |
| Lung fibrosis | 35/113 (31) | 34/115 (30) |
| Impaired lung function | 7/111 (6) | 1/115 (1) |
| Dysphonia | 12/111 (11) | 9/114 (8) |
| Pulmonary hypertension | 2/107 (2) | 4/112 (4) |
| Cardiovascular damage | 21/115 (18) | 30/115 (26) |
| Hypertension | 20/114 (18) | 29/115 (25) |
| Ventricular dysfunction | 0/113 (0) | 5/115 (4) |
| Myocardial infarction | 2/110 (2) | 4/114 (4) |
| Angina | 0/102 (0) | 1/108 (1) |
| Peripheral vascular damage | 7/114 (6) | 6/115 (5) |
| Tissue pulp loss | 3/114 (3) | 1/115 (1) |
| Digit loss | 0/114 (0) | 0/115 (0) |
| Thrombosis | 3/113 (3) | 5/115 (4) |
| Claudication | 1/106 (1) | 0/114 (0) |
| Endocrine damage | 35/114 (31) | 30/110 (27) |
| Diabetes | 5/110 (5) | 11/110 (10) |
| Hirsutism | 4/106 (4) | 5/106 (5) |
| Amenorrhea | 16/98 (16) | 12/102 (12) |
| Irregular menses | 14/100 (14) | 12/100 (12) |
| Infertility | 13/100 (13) | 7/106 (7) |
| Sexual dysfunction | 17/96 (17) | 18/103 (18) |
| Ocular damage | 9/111 (8) | 21/114 (18) |
| Cataract | **7/111 (6)** | **18/114 (16)**** |
| Vision loss | 4/111 (4) | 6/114 (5) |
| Infectious damage | 10/114 (9) | 10/109 (9) |
| Chronic infection | 5/114 (4) | 5/108 (5) |
| Multiple infections | 5/113 (4) | 5/108 (5) |
| Malignancy damage | 4/110 (4) | 6/109 (6) |

* At least 1 item present in each domain of MDI extent of damage score.
** P value = 0.04.

Chi-square or Fisher's exact tests were used to compare the number of patients with a scored Damage item at index date vs 5 years follow up.

Growth failure and delay in secondary sexual characteristics was not considered as these items are only registered in juvenile dermatomyositis.

DM-specific autoantibody subgroup developed less muscle damage than the other groups. Moreover, DM-specific autoantibodies, except for anti-MDA5, are associated with a low frequency of lung disease and dysphagia, which could explain the lower progression of damage over time in the extramuscular domain. The anti-PM/Scl subgroup had the highest MDI score at index date. Notably, this group did not have a higher frequency of any of the 10 most frequent items of MDI score but had higher frequency of other items such as calcinosis compared to the other subgroups. This suggests that this group has a special high risk of accruing early organ damage compared with other autoantibody-defined subgroups. As another example of differences in the pattern of damage, more patients in the IMNM subgroup had persistent muscle weakness, muscle atrophy, and muscle dysfunction at the index date than the other subgroups. These findings are in line with

**Table 4**
Results of the general linear mixed model for prediction of MDI extent score over time.

| Variable | β coefficient | 95 % CI* | P value |
|---|---|---|---|
| Intercept** | 3.68 | 3.33, 4.01 | **<0.001** |
| ASSD group | −0.31 | −0.88, 0.25 | 0.28 |
| DM specific | −0.29 | −0.96, 0.37 | 0.38 |
| IMNM | −0.39 | −1.41, 0.62 | 0.44 |
| MAA | 0.63 | −0.18, 1.44 | 0.13 |
| PM/Scl | 0.09 | −0.80, 0.99 | 0.84 |
| Sex[a] | −0.13 | −0.49, 0.27 | 0.57 |
| Time since diagnosis (years) | 0.16 | 0.11, 0.20 | **<0.001** |
| Age at diagnosis | 0.04 | 0.03, 0.05 | **<0.001** |
| ASSD*Time since diagnosis | −0.03 | −0.10, 0.03 | 0.38 |
| DM specific*Time since diagnosis | −0.08 | −0.16, −0.001 | **0.04** |
| IMNM*Time since diagnosis | 0.04 | −0.11, 0.10 | 0.38 |
| MAA*Time since diagnosis | −0.12 | −0.23, −0.03 | **0.01** |
| PM/Scl*Time since diagnosis | 0.12 | 0.01, 0.22 | **0.03** |

* 95 % of confidence intervals.
** The estimated intercept coefficient is the expected MDI extent of score for the seronegative group, in women, with an average time of follow-up, and with average age at diagnosis.
[a] Women as reference group.
Model based on 2066 observations from 701 patients.
ASSD: antisynthetase syndrome, DM-specific: dermatomyositis specific, IMNM: immune-mediated necrotizing myopathy, MAA: myositis-associated autoantibodies.

several studies that reported poor outcomes in this subgroup of IIMs [24, 25].

In our cohort, the mixed model regression for repeated measurements revealed that trajectories of damage over time were different between the autoantibody-defined subgroups. Compared to the seronegative subgroup as reference, the DM-specific autoantibodies subgroup accrued less damage (MDI extent score) per each year of follow-up since diagnosis, and the anti-PM/Scl subgroup had accrued more damage (MDI extent score) for each year of follow-up since diagnosis . There was no difference in disease duration between the autoantibody-defined subgroups and therefore the difference in the trajectories was considered not attributed to disease duration. Patients positive for anti-PM/Scl have been proposed to represent a separate syndrome, also known as scleromyositis, which may show specific clinical features, including calcinosis, sclerodactyly, esophageal symptoms, and interstitial lung disease [2]. Some studies suggest that these patients may have a good prognosis for lung disease; however, the evidence is inconclusive. For instance, fewer anti-PM/Scl-positive patients had interstitial lung disease at disease onset than ASSD patients; however, one study reported that 61 % of anti-PM/Scl-positive patients developed lung disease during the 5-year follow-up [26]. Another longitudinal study of anti-PM/Scl-positive patients (median follow-up 3.5 years) showed that 10 % of patients with lung disease achieved remission and 70 % improved their pulmonary function; nevertheless, 85 % had a chronic continuous course [27]. In our study, 30 % ($n = 17/56$) of anti-PM/Scl-positive patients had lung fibrosis at the index date, and no patient had this damage at five years of follow-up ($n = 0/7$). These findings suggest that anti-PM/Scl patients with lung fibrosis may have had an ominous prognosis (e.g., death). Unfortunately, we did not have sufficient available information to draw more accurate conclusions. Thirty percent of patients with anti-PM/Scl had dysphagia at the index date and at the 5-year follow-up, with no differences in frequency compared with the other subgroups. In a previous study based on the MYONET registry, dysphagia occurred more often in patients with coexisting systemic sclerosis (OR 3.31) than the remainder of the cohort [28]. In the current study, only 16 % of anti-PM/Scl-positive patients fulfilled the criteria for systemic sclerosis, making it less likely that chronic dysphagia could be explained only by the presence of a systemic sclerosis phenotype. Our findings seem to indicate that the anti-PM/Scl autoantibody could define an often-overlooked group of patients at risk of developing a high rate of

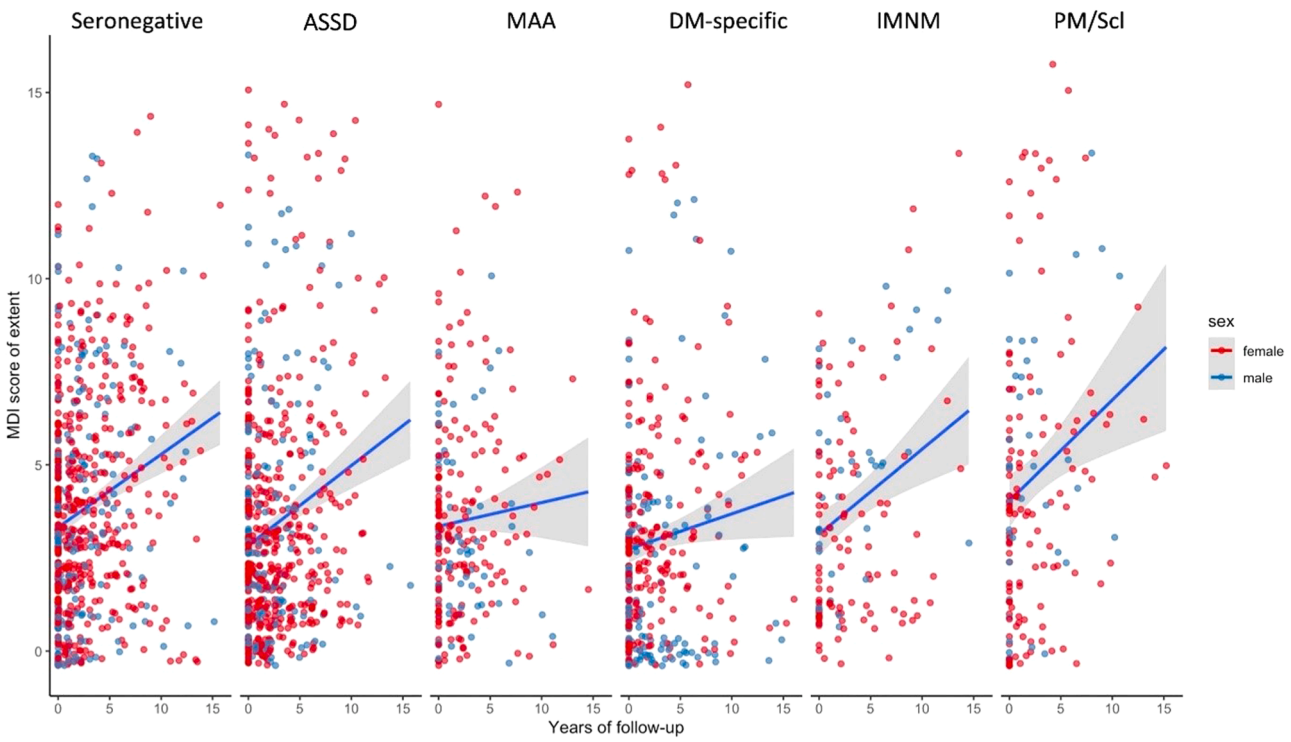


**Fig. 4.** Predicted trajectories of the Myositis Damage Index extent score by the autoantibody-defined subgroups and by sex.
Legend. Each point represents a patient. The blue lines represent the predicted trajectory of the change on the MDI score of extent using linear regression. The grey shadow represents the confidence interval. Years of follow-up since the index date. Note: MAA: myositis associated autoantibodies, IMNM: immune-mediated necrotizing myopathies, DM-specific: dermatomyositis specific autoantibodies, ASSD: Antisynthetase syndrome.

yearly accumulated damage.

We found weak to strong correlations between the severity of muscular damage and functional disability measured using the HAQ-DI, depending on the autoantibody status. At the index date, the seronegative subgroup and the IMNM subgroup had a weak correlation between the severity score of muscular damage and HAQ-DI score; however, at five years of follow-up, this correlation was moderate to strong. These results indicate that it may be difficult to predict the severity of damage at early follow-up using autoantibody status; however, at late follow-up, it may be possible. The effects of other confounders, such as age and disease duration, were not included in the correlation analyses, which is a limitation of this study.

In our study, we could not determine whether the observed damage was due to the disease or its treatment according to the definition of the MDI score. We could not rule out an adverse effect of treatment, in particularly high doses of glucocorticoids, on certain MDI items (e.g., diabetes mellitus, avascular necrosis of the femur, cataract, and osteoporosis with fracture). A longitudinal study (median 2.9 years) showed that the number of new-onset vertebral fractures was associated with higher MDI scores and with previous vertebral fractures, with no differences between clinical subtypes of myositis [29]. Another prospective study reported that glucocorticoid-related morbidity reflected by the presence of vertebral fractures and avascular necrosis of the femur can contribute to progressive functional disability in patients with myositis [30]. Patients with other systemic inflammatory disorders, such as systemic lupus erythematosus (SLE) and anti-neutrophil cytoplasmic antibody-associated vasculitis, tend to experience treatment-related damage over time during long-term follow-up [31,32]. For example, a study in patients with SLE found an independent association between a high accumulated glucocorticoid dose and damage accrual, even in damage items not usually attributed to the use of glucocorticoids (i.e., all items except for avascular necrosis, osteoporotic fractures, diabetes mellitus, and cataracts). However, patients with damage to non-glucocorticoid related items had also registered higher disease activity, which might have confounded the association between the use of glucocorticoids and damage in non-glucocorticoid items, making it difficult to draw conclusions [33]. Similarly, our study showed that some forms of damage tended to develop during late follow-up and may be attributable to treatment or age. Another interesting finding in our study was that certain domains, such as impaired lung function, may be susceptible to improvement by intensive treatment and implementing an exercise program, while other forms of damage, such as lung fibrosis, may remain unchanged or worsen, possibly due to irreversible fibrous tissue or side effects of pharmacological drugs. We did not have information on pharmacological and non-pharmacological treatment available for further analysis. Together, these considerations suggest that damage is a multifactorial dynamic process.

Our study has some limitations, which are expected in any observational registry-based study. First, we excluded a high number of patients who had unknown autoantibody status as it was not registered in MYONET; however, we consider that the population included in our study is highly representative of IIM based on demographic, clinical, and autoantibody status. Second, many patients were lost to follow-up for unknown reasons. However, the proportion of patients in each autoantibody subgroup remained similar at index date and at after five years of follow-up. In addition, even after conducting two sensitivity analyses of our fitted mixed models, the results were similar and provided robust estimates. Regarding myositis-associated cancer, the missing data makes it difficult to assess if the presence of this condition played a role in the outcome i.e., accrued damage; therefore, the interpretation of the causes of loss of follow-up became extremely uncertain. Third, other possible confounding factors were not completely available owing to missing data, such as death, cause of death, exercise, and treatment. Due to missing data, we were not able to perform any analysis for mortality rates, neither for frequency nor for associations with any explanatory variable. Fourth, although the included patients had been initially registered based on clinical diagnosis, we applied the EULAR/ACR criteria, which have shown good performance in a large monocentric

cohort [34]. Moreover, to minimize the risk of excluding patients with an actual diagnosis but not fulfilling the criteria, we included seropositive patients even if the probability of myositis was $\leq$ 50 % ($n$ = 116/757, 15 %). Fifth, analyses for individual autoantibody specificities were not conducted due to the small number of patients in certain subgroups, for example, anti-MDA5 or -HMGCR. However, reports suggest that autoantibody-defined groups may represent a more accurate way to classify patients in terms of clinical disease activity features and prognoses [35]. These last two considerations support our rationale for focusing on autoantibody-defined subgroups rather than of clinically defined subgroups. Finally, different assays for serological testing were used because of the lack of consensus for conducting autoantibody tests, which makes standardization difficult.

In conclusion, our study describes the patterns and trajectories of changes in damage over time in a large international multicenter cohort of patients with IIMs depending on their autoantibody status. At early follow-up, i.e., index date, patients with anti-PM/Scl autoantibodies scored a greater extent of damage, and those with DM-specific autoantibodies had less damage compared with the other subgroups. Regarding trajectories of accrual damage, patients with anti-PM/Scl autoantibodies developed more yearly damage whereas patients with DM-specific autoantibodies developed less yearly damage than the seronegative subgroup as reference. In addition, the severity of damage was associated with functional disability, and this association became stronger over time; at five years of follow-up, patients with IMNM autoantibodies and seronegative patients developed more severe muscle damage, which translated into higher levels of functional disability. These findings suggest that autoantibodies may be useful markers of long-term damage.

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## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Ingrid E Lundberg, Louise Diederichsen reports a relationship with Boehringer Ingelheim Pharmaceuticals Inc that includes: consulting or advisory. Ingrid E Lundberg reports a relationship with Astra Zeneca that includes: board membership. Ingrid E Lundberg, Jiri Vencovsky, reports a relationship with EMD Serono Inc that includes: funding grants. Ingrid E Lundberg, Marianne de Visser reports a relationship with Novartis that includes: consulting or advisory. Ingrid E Lundberg reports a relationship with Pfizer that includes: consulting or advisory. Ingrid E Lundberg reports a relationship with Janssen Pharmaceuticals Inc that includes: consulting or advisory. Hector Chinoy reports a relationship with UCB Inc that includes: speaking and lecture fees. Hector Chinoy reports a relationship with GlaxoSmithKline Inc that includes: speaking and lecture fees. Ingrid E Lundberg, Louise Diederichsen reports a relationship with Boehringer Ingelheim Pharmaceuticals Inc that includes: speaking and lecture fees. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2024.152529.

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