Clinical heterogeneity based on race and sex within a large cohort of inclusion body myositis patients

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ABSTRACT

Background and Objectives: Sporadic inclusion body myositis (IBM) is the most
common acquired myopathy in individuals over age 50. The disorder is slowly
progressive and while many therapies have been investigated, response has generally
been poor. Clinical heterogeneity may influence treatment responsiveness; however,
data regarding heterogeneity in IBM is limited and often conflicting. We aim to identify
clinically distinct subgroups within a large IBM cohort, as well as prognostic factors for
disease progression.

Methods: Clinical, histologic, radiologic, and electrophysiologic data were analyzed for
all patients with IBM and other forms of myositis enrolled in a longitudinal cohort from
The Johns Hopkins Myositis Center from 2003-2018. Univariate, multivariate, and
graphical analyses were used to identify prognostic factors in IBM patients.

Results: Among the 335 IBM patients meeting inclusion criteria, 64% were male with
an average age of disease onset of 58·7 years and a delay to diagnosis of 5·2 years.
Initial misdiagnosis (52%) and immunosuppressant treatment (42%) were common.
Less than half (43%) of muscle biopsies demonstrated all three pathologic hallmarks:
endomysial inflammation, mononuclear cell invasion, and rimmed vacuoles. Black
patients had significantly weaker arm abductors, hip flexors, and knee flexors compared
to non-Black patients but were less likely to develop dysphagia. Female patients had
stronger finger flexors and knee extensors compared to their male counterparts but
were more likely to develop dysphagia. A significant number (20%) of patients had an
age of onset less than 50 years. This group of younger patients was weaker at their first
visit; however, this may be accounted for by a longer disease duration at first visit.

Discussion: Although IBM has long been considered a disorder predominately of older, White men, female, and non-White patients comprise a significant proportion of the IBM population. Our study demonstrates that female and Black patients have distinct clinical phenotypes within the overarching IBM clinical phenotype.

INTRODUCTION

Sporadic inclusion body myositis (IBM) is the most common acquired myopathy among individuals older than 50 years of age. Gradual progression of muscle weakness and atrophy, particularly of the finger flexors and quadriceps muscles, and muscle biopsies showing endomysial inflammation with auto-invasive T-cells and rimmed vacuoles are hallmarks of the disease. Although there is evidence for dysregulation of the immune system in IBM, multiple trials of immunosuppressive agents have failed to show a benefit.[1–5] Both degenerative and neoplastic processes have been suggested as alternative mechanisms.[6,7]

Of the relatively few studies that have closely examined the clinical symptoms and course of IBM, most have investigated small cohorts (mean 47 patients) with limited follow-up (mean 2·3 years).[8–16] Although these studies have described an overall consistent IBM phenotype, there is evidence of substantial variability both within and between studies as regards presentation, clinical progression, and accumulation of debility. While the majority of patients in these studies had an age of onset in their late fifties, a considerable number (5-20%) developed symptoms at less than 50 years of age. Onset of weakness in the lower extremities was most common, however onset in the upper extremities was reported in 10-20% of patients and onset in the bulbar muscles in 5-10% of patients. About half of patients overall developed dysphagia during their disease course, and there was considerable variability in the progression of weakness in other skeletal muscles both between muscle group and individual patients

Most patients eventually required the use of an assistive device for ambulation, however there was a wide range in the time from diagnosis to the need for an assistive device (range 6-16 years). Data on mortality was mixed with some studies showing increased mortality in IBM patients, often related to respiratory causes,[16–18] whereas others demonstrated no impact of IBM on mortality.[11,12]

Data on prognostic factors has likewise been limited and often conflicting. Several studies have shown a more rapid functional decline in patients with older age of onset.[9–11,14] However, others found mixed results[13,19] or no correlation between age of onset and progression of weakness,[12] and one study reported a more rapid decline in pinch strength among individuals with a younger age of onset.[15] Oldroyd et al reported a more rapid decline in pinch and knee extensor strength in men, however, sex was not found to have an association with strength decline in other studies.[12,13] The presence of anti-NT5c1A autoantibodies has also been reported as a poor prognostic factor in some studies,[15,20] although in others, no correlation was seen between seropositivity and prognosis.[21,22]

These studies suggest that IBM is a much more heterogeneous condition than has previously been considered. A larger study of IBM is important to identify distinct subgroups of IBM patients and the prognostic factors that may influence their clinical trajectory. Such information can better inform patients about their expected disease course and can influence the design of clinical trials. We conducted a prospective

longitudinal cohort study of 335 IBM patients followed at the Johns Hopkins (JH) Myositis Center to identify IBM subgroups and their associated prognostic indicators.

METHODS

Patients

All patients who provided informed consent to be enrolled in the JH Myositis Center Registry between 2003 and 2018 with a diagnosis of sporadic IBM were reviewed. All patients were evaluated by a JH Myositis Center physician. Those meeting at least one of the following criteria were included for analysis: Griggs possible, European Neuromuscular Centre (ENMC) 2011 probable, or Lloyd-Greenberg data-derived criteria (DDC) for IBM.[23–25] We included as comparators all those myositis patients that were positive for autoantibodies recognizing Mi-2, NXP-2, TIF1-γ, MDA-5, Jo-1, PL-7, PL- 12, SRP, or HMGCR by at least two different techniques from among the following: ELISA, immunoprecipitation of *in vitro* transcribed and translated protein, line blotting (EUROLINE myositis profile), and immunoprecipitation from S35-labeled HeLa cell lysates (S35 IP). Comparators were included in the dermatomyositis (DM) group if they had autoantibodies recognizing Mi-2, NXP-2, TIF1-γ, or MDA-5. Alternatively, patients were classified as having Antisynthetase Syndrome (AS) if they had autoantibodies against Jo-1, PL-7, or PL- 12. Patients were included in the Immune-mediated Necrotizing Myopathy (IMNM) group if they tested positive for anti-SRP or anti-HMGCR autoantibodies.[26]

Investigations

All clinical assessments were performed by either a JH Myositis Center physician or another neuromuscular specialist at The Johns Hopkins University. Disease onset was defined as the time of onset of the initial symptom (presenting symptom) leading to a diagnosis of IBM. Date of diagnosis was defined as the date the diagnosis of IBM was made by a treating physician. Dates were derived as patient-reported or as otherwise noted in the medical record. If a specific date (MM/DD/YYYY) of onset or diagnosis was not available, the midpoint of the specified month or year was selected for the purposes of statistical analysis. Time to diagnosis was defined as the time interval between disease onset and IBM diagnosis date. Disease duration to first visit was defined as the time interval between disease onset and first visit to the JH Myositis Center. Initial symptoms and initial diagnoses other than IBM were derived as patient-reported or as otherwise noted in the medical record.

Manual muscle testing was recorded using the Medical Research Council (MRC) scale and converted to a ten-point Kendall scale for analysis. Manual muscle testing from the first JH Myositis Center visit was utilized for analysis in this study. The presence of dysphagia was assessed throughout the study based upon patient report of symptoms. Sera from a subset of IBM patients were tested for anti-NT5C1a antibodies by ELISA (ELISA MUP-44 [NT5C1A] Catalog #1675-4801G). Only electrodiagnostic studies performed at JH by an experienced electromyographer were included in this study. Conventional techniques were employed and JH electrodiagnostic laboratory normal values were utilized for analysis. The presence of peripheral neuropathy was defined as a sural sensory nerve action potential (SNAP) amplitude of < 9 µV. Muscle biopsy

reports from both Johns Hopkins and outside institutions were included. Reports were
reviewed by JH Myositis Center physicians and considered sufficient for diagnostic
purposes if cardinal IBM histopathologic features were assessed. A subset of reports
containing more detailed histopathologic descriptions was included for further analysis.

Statistics

Dichotomous variables were expressed as percentages and absolute frequencies, and
continuous features were reported as means and standard deviations (SD). Pairwise
comparisons for categorical variables between groups were made using the chi-square
test or Fisher's exact test, as appropriate. The Student's t-test was used to compare
continuous variables among groups. CK, a highly positively skewed variable, was
expressed as median, first, and third quartile for descriptive purposes. Linear and
logistic regressions were used to adjust for potential confounding variables.
Indirect standardization was used to compare mortality in IBM patients compared to the
general population as described elsewhere.[27]

To account for the different number of visits per patient, the evolution of CK levels and
muscle strength was studied using multilevel linear regression models with random
slopes and random intercepts. Non-modifiable risk factors (sex, race, disease duration,
and age at the onset of first symptoms) were used as adjusting covariates for the
multivariate analysis. Generalized additive models (GAM) were applied to graphically
analyze the longitudinal changes in strength and CK levels. All statistical analyses were

performed using Stata/MP 14.1, and R v.4.0.3. A 2-sided p-value of 0.05 or less was considered significant with no correction for multiple comparisons.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by an institutional review board at The Johns Hopkins Hospital. Written informed consent was obtain from all participants at the time of their enrollment in the JH Myositis Center Registry.

Data availability

De-identified data, study protocol and statistical analysis plan will be made available in the case of a reasonable request providing that the proposed use of the data has been approved by an independent review committee and that investigators meet The Johns Hopkins University policies for data sharing and management.

RESULTS

Patient Characteristics

Clinical Criteria: Within the JH Myositis Center Registry, a total of 387 patients were identified with a listed diagnosis of IBM. Of these, 335 met at least Griggs possible, ENMC probable, or DDC criteria for IBM and were included in the subsequent analysis. Only a small percentage of IBM patients met either Griggs definite (2%) or ENMC clinico-pathologically defined (1%) criteria (Supplementary Table 1). This was primarily due to the lack of electron microscopy and evaluation for protein accumulations other

than amyloid in routine muscle biopsy assessments. Nearly half of patients (46%) met criteria for Griggs, ENMC, and DDC, with 16% meeting only ENMC criteria, 15% meeting only DDC criteria, and 16% meeting both ENMC and DDC criteria (Figure 1).

An additional 524 patients with other forms of autoimmune myositis were identified as a comparator group. These included 165 patients with IMNM, 199 patients with DM, and 160 patients with AS.

IBM Clinical Characteristics: Baseline clinical information for the overall cohort are summarized in Supplementary Table 2. Compared with other types of myositis, IBM was more common in male (64%, p<0·001), White (84%, p<0·001), and older patients (median age at onset 58·7, p<0·001). The average time to diagnosis for IBM was longer than for other myositis groups (5·2 years, p<0·001). Only 4% of IBM patients reported dysphagia as a presenting symptom, which was less than IMNM (19%, p<0·001) or DM (19%, p<0·001). However, 60% developed symptoms of dysphagia during the course of their illness, which was significantly higher compared to patients with IMNM (45%, p=0·007) or the antisynthetase syndrome (38%, p<0·001) but not dermatomyositis (53%, p=0·99). A considerable number of patients (42%) were treated with immunosuppressive agents, although this was lower than any other type of myositis (p<0·001) in our study. Corticosteroids and methotrexate were the most common agents utilized. Compared with the other clinical groups, the overall mortality rate was higher in IBM than in IMNM; however, there were no significant differences in mortality between IBM and the general population (SMR 1·15, 95%CI 0·71-1·75).

Compared to patients with other types of myositis, those with IBM had more severe

finger flexor and knee extensor weakness (Supplementary Table 3), showing a steady

decline (about 0·33 Kendall scale strength-points per year) in these two muscle groups

during the evolution of their disease (Figure 2). In contrast, hip flexors and arm

abductors tended to be stronger in IBM than in IMNM during the first 10 years after the

onset of the disease (Figure 2).

Over half of IBM patients received an initial diagnosis other than IBM (Supplementary

Table 4). The most common misdiagnoses were polymyositis (22%) and unspecified

myopathy (13%). Patients with initial misdiagnoses were more likely to be female and to

have a younger age at disease onset. Finger flexor weakness and rimmed vacuoles on

muscle biopsy were less common in this group. Those with an initial diagnosis of

polymyositis were more likely to be ANA positive compared to those initially diagnosed

with IBM (50% versus 31%, p=0·04).

IBM Ancillary Testing: The average duration of disease at the time of muscle biopsy

was 5·5 years. The combination of endomysial inflammation, invasion of non-necrotic

fibers, and rimmed vacuoles was seen in 43% of biopsies. An additional 41% contained

at least two of these cardinal features, and 34% did not show rimmed vacuoles (Figure

3). The quadriceps muscle was the most common muscle selected for biopsy. The

location of the muscle biopsy did not influence the number of pathologic features

present, except for the more common presence of COX-negative fibers in the biceps (82%) or deltoid (83%) muscles compared to the quadriceps (47%).

Electrodiagnostic data was available for 285 (85%) IBM patients (Supplementary Table 5). Myopathic motor unit action potentials (small duration and small amplitude) were seen in nearly all patients with 44% also showing neurogenic units (large duration and large amplitude). Abnormal sural SNAP amplitudes (< 9 µV) were present in 46% of IBM patients compared to 24% of patients with other forms of myositis. However, multivariate analysis suggested that this difference may be accounted for by the older age of IBM patients at the time of EMG. The median CK in our IBM cohort was 426 IU/L with a Q1-Q3 range of 230-707 IU/L. A positive ANA was found in 40% of patients tested (n=199). Testing for the anti-NT5c1A autoantibody was performed by ELISA for 320 IBM patients. Forty-seven percent were positive for this autoantibody.

IBM Heterogeneity

Race: Compared to other races, Black IBM patients were younger at the time of their first JH Myositis Center visit although this did not reach statistical significance. Black patients had significantly weaker arm abductors, hip flexors, and knee flexors (Table 1) at the first JH Myositis Center visit. They were less likely to report dysphagia during their disease course (45%) compared to non-Black patients (61%, p = 0·05). Black patients were more likely to have been misdiagnosed with polymyositis and treated with immunosuppressive agents. The median CK was higher in this group (676 IU/L, Q1-Q3 range 496-1035 IU/L) and neuropathic motor units were less commonly observed in

electrodiagnostic studies (20%). Anti-NT5c1A autoantibodies were more commonly detected among Black patients (68%, p=0·02). There was no difference in muscle biopsy features across races.

Multilevel regression models (independent of all the above-mentioned potential confounding factors) confirmed that Black patients had more severe weakness of hip flexors (-2·1 strength-points, p<0·001), arm abductors (-0·6 strength-points, p=0·02), and knee extensors (-1·3 strength-points, p=0·02), and had a trend toward weaker finger flexor muscles (-1·1 strength-points, p=0·06). It also confirmed that Black IBM patients have higher CK levels (p=0·001). Logistic regression showed that Black patients had lower odds of developing dysphagia (OR 0·4, p=0·05).

Female Sex: Women had a longer time to diagnosis and were more likely to have been misdiagnosed with polymyositis than men (Table 2). Corticosteroid use was more common in women, although overall use of immunosuppressants did not differ between the sexes. Strength profiles showed that women had stronger knee extensors (p=0·003) and a trend towards having stronger finger flexors (p=0·06) (Figure 4). Women were more likely to develop dysphagia during their disease course (69%) compared to their male counterparts (55%, p = 0·02). Myopathic units were equally common between the sexes, although women tended to have less abnormal spontaneous activity on EMG.

Multilevel regression models confirmed that women have stronger finger flexors (0·8 strength-points, p=0·02) and knee extensor muscles (0·9 strength-points, p=0·009) with

no significant difference in hip flexor or arm abductor strength (both p>0·05). CK was lower in females (p=0·02). Logistic regression showed that females develop dysphagia more frequently than males (OR 1·8, p=0·02).

Age at Onset: Patients with a younger age at onset had a longer time to diagnosis and time to referral to the JH Myositis Center. Those with onset at < 50 years were also more likely to be initially misdiagnosed with polymyositis and treated with immunosuppressive therapy, especially methotrexate, mycophenolate, and IVIG. Muscle biopsy features did not differ between the age groups, although patients with a younger age at onset had a significantly longer disease duration at the time of biopsy, 7.3 years for the < 50 age group versus 2.9 years for the > 70 age group.

On univariate analysis, younger-onset patients had a more severe and diffuse pattern of weakness at the first visit, including more profound proximal weakness (Table 3). However, multivariate regression models demonstrated that this difference was driven by the longer disease duration at the first visit in the younger-onset age group. Older age at onset was associated with lower median CK levels (p<0·001). Logistic regression showed that there was no association between the prevalence of dysphagia and the age at onset, but there was a strong association between older age at onset and abnormal sural SNAP amplitudes (p<0·001).

NT5C1A Status: Anti-NT5C1A-positive patients had higher median CK levels, but antibody status did not otherwise influence clinical characteristics, the pattern of weakness, muscle biopsy features, or electrodiagnostic findings.

DISCUSSION

This study, including 335 IBM patients, is the largest cohort study of sporadic IBM to date. The general characteristics of our IBM cohort are similar to those previously reported, indicating that our findings are generalizable to the IBM population at large. Importantly, however, our large cohort also included significant numbers of female and Black patients, as well as patients with an age at onset < 50 years. These subpopulations have not been well described in the IBM literature to date, and few prior cohort studies have assessed the clinical phenotype in these IBM patient subpopulations. Although both Black and female patients demonstrated an overall pattern of weakness consistent with that typically seen in IBM, Black patients had significantly weaker proximal muscles and female patients had less prominent knee extension and finger flexion weakness. These characteristics may explain why both patient populations were more likely to be initially misdiagnosed with polymyositis and to be treated with corticosteroids.

Patients with an age of symptom onset < 50 years had more diffuse and severe weakness at the initial JHH visit compared to their older onset counterparts. However, this effect was confounded by a longer disease duration at the time of the first visit in

the younger-onset group. Adjusting by this factor, we found that IBM patients with onset at an older age had more severe weakness in finger flexors, while other muscles showed similar levels of weakness. Other studies have reported more rapid progression in patients with an older age of onset, though this was not observed in our cohort.[9–11,14]

These findings suggest that Black and female patients may represent clinically distinct subgroups within IBM with unique disease trajectories and, potentially, different responses to therapeutic interventions. Although a distinct pattern was not confirmed in patients with a younger age at onset, our analysis was limited by constraining clinical assessments to visits at the JH Myositis Center. Thus, it is possible that this population did have a unique pattern of disease at onset which may be less prominent with more advanced disease.

In accordance with prior studies, a large percentage of our patients experienced a prolonged time to diagnosis, during which period many were initially misdiagnosed with polymyositis and treated with ineffective immunosuppressive therapies. We suspect that over-reliance on muscle biopsy features and under-reliance on physical exam (e.g. presence of finger flexor weakness and quadriceps>hip flexor weakness patterns) are major factors in the long delay to diagnosis that is common for IBM patients. Only 43% of muscle biopsies in our study contained all three cardinal features of IBM (endomysial inflammation, mononuclear cell invasion, and rimmed vacuoles). In particular, rimmed vacuoles were less common in our study (66%) compared to prior studies (75-100%).[8,11,14] This likely reflects the increased reliance of Griggs and ENMC criteria for

inclusion in prior published reports, both of which required the presence of rimmed vacuoles to meet definite or clinicopathologically defined IBM, respectively. This highlights the need for more accurate and less invasive diagnostics to identify IBM patients at earlier stages of disease when they may be more responsive to therapeutics.

Many of our patients also had electrodiagnostic evidence of peripheral neuropathy as defined by decreased sural SNAP amplitudes. Although a few small studies have reported evidence of peripheral nerve dysfunction in up to 30% of IBM patients, the involvement of peripheral nerves has not been extensively studied.[28,29] In the current study, we found evidence of axonal loss in 46% of IBM patients, well beyond the reported estimates of peripheral neuropathy in the general population (2-8%).[30] However, when compared with patients with other forms of autoimmune myositis, the prevalence of sural SNAP abnormalities was found to be driven by the older age at EMG/NCS rather than by the presence of IBM. Detailed studies of electrodiagnostic data in IBM are needed to explore this further.

Our study has several limitations. Data from clinical assessments were constrained to visits at the JH Myositis Center at which point patients had had symptoms for 6.6 years on average. Although female and Black IBM patients did have different patterns of weakness by this time, their initial symptoms may have differed more dramatically. In addition, younger-onset patients may have had a distinct phenotype at presentation which became obscured by more advanced disease.

In conclusion, sporadic IBM has long been considered a disease predominately affecting older White men. Our cohort included a significant number of female, Black, and younger-onset patients and demonstrated a unique clinical profile in both female and Black patients that may explain the propensity for initial misdiagnosis and ineffective immunosuppressant agent use in these populations. Further longitudinal studies are needed to confirm and further characterize these findings; however, it is important to recognize the presence of these subgroups as they may have different responses to therapies, and their presence may influence the design of future clinical trials in IBM. More sensitive and accessible diagnostics are needed to identify IBM patients at earlier stages and within these less well-recognized subpopulations to further our understanding of clinical heterogeneity within this disorder.

Acknowledgements

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Figure 1. Overlap of diagnostic criteria in a large IBM cohort.
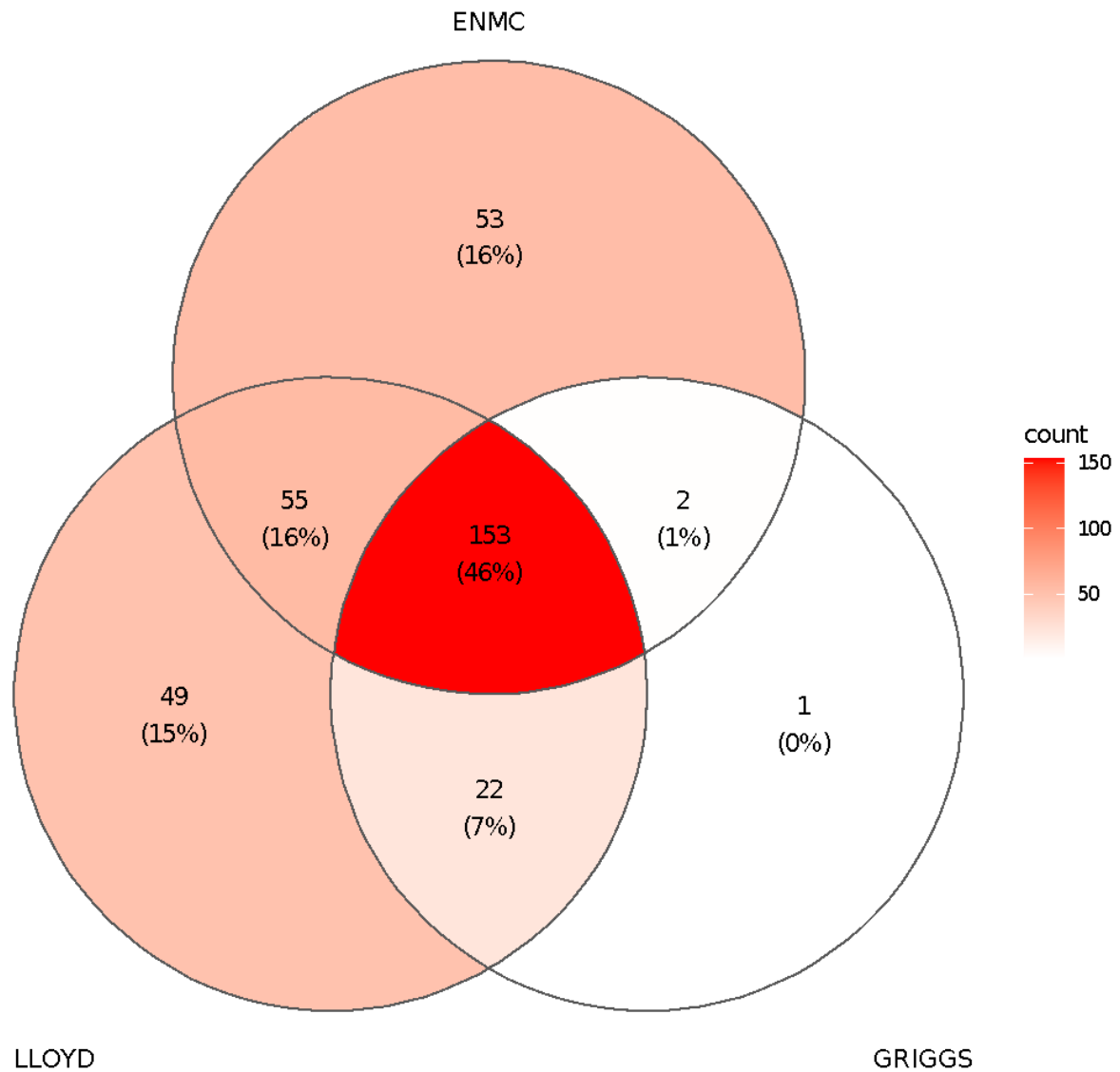
ENMC: European Neuromuscular Centre criteria; GRIGGS: Griggs criteria; LLOYD: Data-Derived Criteria (also referred to in the literature as Lloyd-Greenberg criteria).

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Figure 2. Evolution of strength in inclusion body myositis compared to other types of autoimmune myositis using generalized additive models.
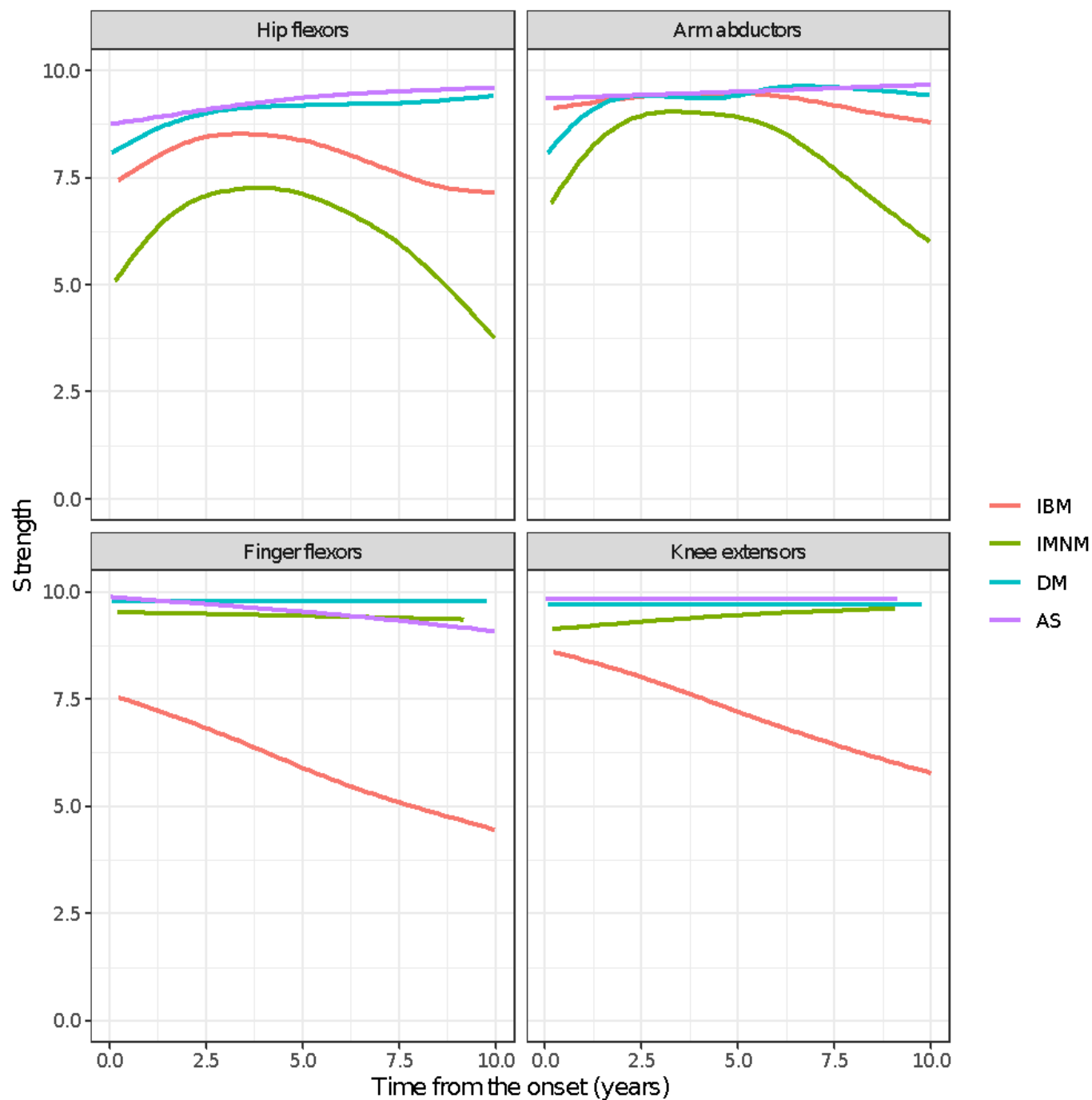
Figure 3. Cardinal IBM muscle biopsy features
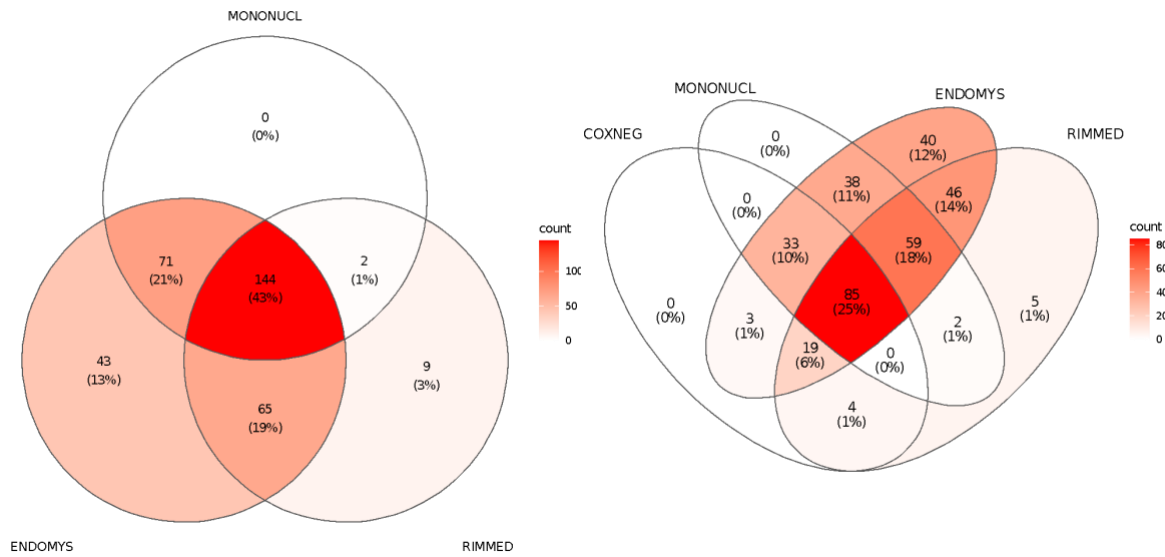
ENDOMYS: Endomysial inflammation. **MONONUCL:** Mononuclear cell invasion of non-necrotic myocytes. **RIMMED:** Rimmed vacuoles. **COXNEG**: Cox-negative fibers.

Table 1. IBM characteristics by race grouping

|	*White* (n=280)	*Black* (n = 29)	*Other Races* (n = 26)
Sex, female	36% (102)	48% (14)	23% (6)
Mean age at symptom onset (yr)	59.0 (9.9)	55.6 (8.4)	59.2 (9.7)
Mean time to diagnosis (yr)	5.4 (4.5)	5.0 (4.7)	3.8 (3.7)
Mean disease duration at first JH visit (yr)	6.8 (5.4)	4.8 (4.4)	6.3 (4.3)
Initial diagnosis			
IBM	48% (127)	45% (13)	59% (13)
Polymyositis	21% (55)	41% (12)**	14% (3)
Immunosuppressant Therapy			
Any Immunosuppressant Agent	40% (111)	62% (18)	42% (11)
Corticosteroids	32% (89)	55% (16)*	31% (8)
Methotrexate	16% (44)*	34% (10)*	23% (6)
Azathioprine	4% (12)*	17% (5)*	8% (2)
Mycophenolate	5% (15)	10% (3)	0% (0)
IVIG	7% (19)*	21% (6)*	12% (3)
Mean muscle strength at first visit†			
Arm Abduction	9.3 (1.5)	8.7 (2.3)*	9.2 (1.7)
Elbow Flexion	9.0 (1.4)	8.7 (2.0)	8.8 (1.7)
Elbow Extension	8.2 (1.5)	8.2 (2.1)	7.6 (2.4)
Wrist Flexion	8.2 (1.8)	7.8 (2.3)	7.8 (2.5)
Wrist Extension	9.2 (1.7)	8.9 (2.1)	9.0 (2.4)
Finger Flexion	5.8 (3.0)	5.9 (2.5)	4.8 (3.1)
Finger Extension	8.8 (1.9)	8.5(2.3)	8.9 (1.8)
Hip Flexion	7.9 (2.2)**	6.1 (3.8)***	7.5 (3.1)
Knee Flexion	9.3 (1.3)**	8.2 (2.7)***	9.2 (1.7)
Knee Extension	7.0 (3.0)*	5.9 (3.4)	6.0 (2.9)
Ankle Dorsiflexion	8.4 (2.5)*	7.3 (3.6)*	7.5 (3.1)
Ankle Plantarflexion	9.3 (1.9)	8.1 (3.3)**	9.7 (1.1)
Serologies			
Median CK (IU/L)	410 (218-684)*	676 (496-1035)***	380 (269-610)
NT5C1A positive	44% (119)	68% (19)*	46% (11)
ANA (+)	40% (68)	44% (8)	23% (3)
Electrodiagnostic Studies			
Irritability	85% (202)	92% (23)	95% (18)
Myopathic Units	92% (217)	96% (24)	95% (18)
Neurogenic Units	46% (108)	20% (5)*	47% (9)
Mixed Units	43% (100)	20% (5)*	47% (9)
Sural SNAP < 9 µV	31% (88)	34% (10)	19% (5)

*p = <0.05, **p = <0.01, ***p = <0.001. † Kendall scale. IBM: Inclusion body myositis. IVIG: Intravenous immunoglobulin. CK: Creatine kinase. NT5C1A: 5'nucleotidase, cytosolic 1A. ANA: Antinuclear antibody. SNAP: Sensory nerve action potential.

Table 2: IBM characteristics by sex grouping

	Male *(n = 213)*	*Female* *(n = 122)*
Mean age at symptom onset (yr)	59.2 (10.1)	58.0 (9.1)
Mean time to diagnosis (yr)	4.7 (4.2)**	6.2 (4.8)**
Mean disease duration at first JH visit (yr)	6.2 (5.2)	7.3 (5.4)
Initial diagnosis		
IBM	55% (110)**	37% (43)**
Polymyositis	17% (34)**	31% (36)**
Immunosuppressant Therapy		
Any Immunosuppressant Agent		
Corticosteroids	30% (63)*	41% (50)*
Methotrexate	15% (33)	22% (27)
Azathioprine	6% (12)	6% (7)
Mycophenolate	4% (9)	7% (9)
IVIG	8% (17)	9% (11)
Mean muscle strength at first visit[†]		
Arm Abduction	9.3 (1.7)	9.2 (1.4)
Elbow Flexion	9.0 (1.5)	8.8 (1.5)
Elbow Extension	8.1 (1.7)	8.2 (1.6)
Wrist Flexion	8.3 (1.7)*	7.8 (2.1)*
Wrist Extension	9.2 (1.8)	9.0 (1.7)
Finger Flexion	5.5 (3.1)	6.1 (2.7)
Finger Extension	8.9 (1.9)	8.8 (1.9)
Hip Flexion	7.7 (2.5)	7.7 (2.4)
Knee Flexion	9.2 (1.6)	9.2 (1.4)
Knee Extension	6.6 (3.2)*	7.4 (2.6)*
Ankle Dorsiflexion	8.1 (2.6)	8.4 (2.7)
Ankle Plantarflexion	9.3 (2.0)	9.1 (2.2)
Serologies		
Median CK (IU/L)	467 (281-770)***	326 (174-522)***
NT5C1A positive	48% (96)	45% (53)
ANA (+)	34% (41)	48% (38)
Electrodiagnostic Studies		
Irritability	92% (166)***	76% (77)***
Myopathic Units	94% (169)	90% (90)
Neurogenic Units	47% (83)	39% (39)
Mixed Units	44% (78)	36% (36)
Sural SNAP < 9 µV	32% (69)	28% (34)

*p = <0.05, **p = <0.01, ***p = <0.001. [†] Kendall scale. IBM: Inclusion body myositis. IVIG: Intravenous immunoglobulin. CK: Creatine kinase. NT5C1A: 5'nucleotidase, cytosolic 1A. ANA: Antinuclear antibody. SNAP: Sensory nerve action potential.

Figure 4. Evolution of strength in inclusion body myositis according to sex using generalized additive models.
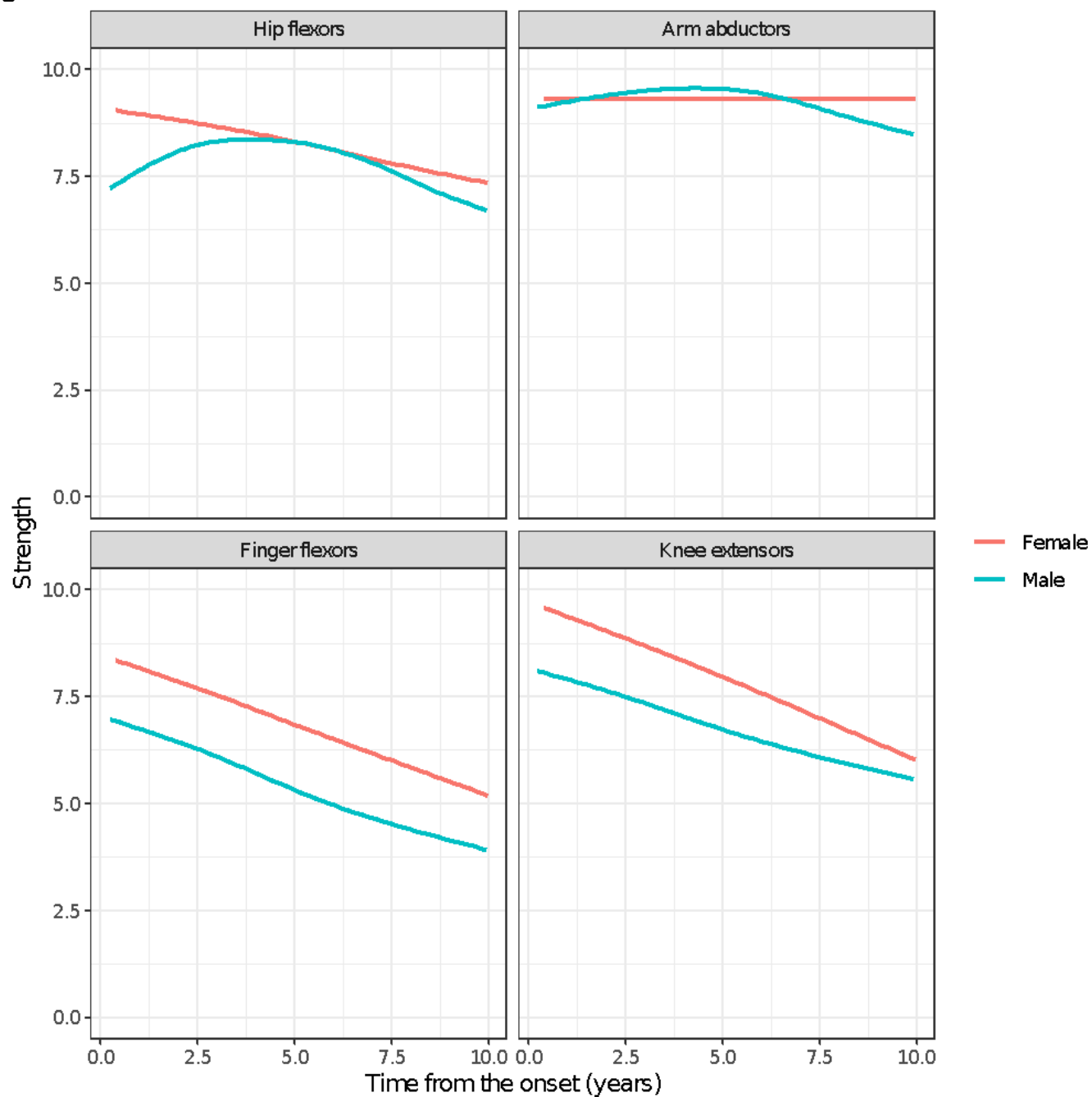
Table 3. IBM characteristics by age of onset grouping

	< 50 yr (n = 66)	*50-61 yr* (n = 117)	*61-70 yr* (n = 102)	*>70 yr* (n = 50)
Sex, male	64% (42)	56% (65)*	69% (70)	72% (36)
Mean age at symptom onset (yr)	44.8 (4.9)***	55.7 (2.8)***	64.3 (2.8)***	74.0 (3.3)***
Mean time to diagnosis (yr)	7.5 (5.7)***	5.8 (4.6)	4.4 (3.3)*	2.5 (1.9)***
Mean disease duration at first visit (yr)	9.2 (7.1)***	7.4 (5.2)	5.6 (3.5)*	2.9 (2.0)***
Initial Diagnosis				
IBM	34% (22)**	51% (54)	52% (51)	55% (26)
Polymyositis	34% (22)*	22% (23)	20% (20)	11% (5)*
Immunosuppressant Therapy				
Any Immunosuppressant Agent	55% (36)*	41% (48)	37% (38)	36% (18)
Corticosteroids	44% (29)	31% (36)	31% (32)	32% (16)
Methotrexate	27% (18)*	17% (20)	14% (14)	16% (8)
Azathioprine	11% (7)	6% (7)	4% (4)	2% (1)
Mycophenolate	14% (9)**	4% (5)	4% (4)	0% (0)
IVIG	15% (10)*	12% (14)	4% (4)	0% (0)
Mean muscle strength at first visit†				
Arm abduction	8.5 (2.5)***	9.3 (1.4)	9.5 (1.0)	9.6 (0.7)
Elbow Flexion	8.2 (2.2)***	9.0 (1.3)	9.1 (1.2)	9.4 (1.7)*
Elbow Extension	7.6 (2.2)**	8.2 (1.5)	8.2 (1.6)	8.6 (1.2)*
Wrist Flexion	7.7 (2.2)*	8.1 (2.0)	8.2 (1.7)	8.8 (1.2)*
Wrist Extension	8.5 (2.5)***	9.2 (1.6)	9.2 (1.7)	9.8 (0.7)**
Finger Flexion	5.1 (3.0)	5.7 (3.2)	5.9 (2.7)	6.2 (3.0)
Finger Extension	8.2 (2.5)**	8.8 (1.9)	8.9 (1.8)	9.5 (0.8)*
Hip Flexion	6.8 (3.3)***	7.9 (2.5)	7.9 (2.2)	8.1 (1.5)
Knee Flexion	9.0 (2.0)	9.2 (1.5)	9.2 (1.5)	9.6 (0.7)*
Knee Extension	6.1 (3.5)*	7.0 (3.0)	6.9 (2.8)	7.6 (2.6)
Ankle Dorsiflexion	7.3 (3.5)**	8.2 (2.7)	8.6 (2.3)	8.7 (1.5)
Ankle Plantarflexion	9.0 (2.6)	9.4 (1.8)	9.1 (2.2)	9.6 (1.3)
Serologies				
Median CK (IU/L)	460 (277-810)	438 (249-720)	430 (227-634)	294 (167-477)**
NT5C1A positive	49% (31)	49% (56)	41% (39)	48% (23)
ANA (+)	45% (17)	34% (22)	34% (23)	57% (17)*
Electrodiagnostic Studies				
Irritability	89% (49)	88% (85)	79% (69)*	95% (40)
Myopathic Units	93% (51)	95% (91)	90% (77)	95% (40)
Neurogenic Units	29% (16)*	43% (41)	48% (41)	57% (24)
Mixed Units	27% (15)*	41% (39)	44% (37)	55% (23)*
Sural SNAP < 9 µV	23% (15)	26% (31)	32% (33)	48% (24)**

*p = <0.05, **p = <0.01, ***p = <0.001. † Kendall scale. IBM: Inclusion body myositis. IVIG: Intravenous immunoglobulin. CK: Creatine kinase. NT5C1A: 5'nucleotidase, cytosolic 1A. ANA: Antinuclear antibody. SNAP: Sensory nerve action potential.

Supplementary Table 1. Patients meeting IBM diagnostic criteria

Diagnostic Criteria	% (n)
Griggs	
Definite	2% (7)
Possible	53% (177)
ENMC 2011	
Clinico-Pathologically Defined	1% (2)
Clinically Defined	53% (177)
Probable	78% (261)
Lloyd-Greenberg	83% (279)

IBM: Inclusion body myositis

Supplementary Table 2. Overall clinical characteristics of inclusion body myositis compared to other types of autoimmune myositis

	IBM	IMNM	Multivariate p-value	DM	Multivariate p-value	AS	Multivariate p-value
	(n=335)	(n=165)		(n=199)		(n=160)	
Female sex	36% (122)	62% (103)***	..	73% (145)***	..	72% (115)***	..
Race							
White	84% (280)	68% (112)***	..	75% (149)*	..	58% (93)***	..
Black	9% (29)	24% (40)***	..	14% (27)	..	31% (50)***	..
Other races	8% (26)	8% (13)	..	12% (23)	..	11% (17)	..
Age at onset (years)	58.7 (9.8)	51.1 (14.6)***	..	47.8 (14.9)***	..	46.1 (12.8)***	..
Time to diagnosis	5.2 (4.5)	1.8 (4.5)***	< 0.001	1.1 (2.0)***	< 0.001	1.1 (1.6)***	< 0.001
Time of follow-up (years)	2.3 (2.8)	3.9 (3.7)***	< 0.001	4.3 (3.6)***	< 0.001	4.6 (3.9)***	< 0.001
Time to first JH visit (years)	6.6 (5.3)	2.4 (3.2)***	< 0.001	1.5 (3.1)***	< 0.001	2.2 (2.9)***	< 0.001
Number of visits per participant	4.2 (4.7)	9.1 (8.9)***	< 0.001	9.6 (7.0)***	< 0.001	9.7 (6.8)***	< 0.001
Death during follow-up	7% (25)	3% (5)*	0.6	5% (9)	0.9	9% (14)	0.09
Dysphagia at onset	4% (12)	19% (31)***	< 0.001	19% (38)***	< 0.001	6% (10)	0.5
Dysphagia during follow-up	60% (201)	45% (74)**	0.007	53% (106)	1.0	38% (60)***	< 0.001
Treatments							
Any immunosuppressant	42% (140)	87% (143)***	< 0.001	96% (192)***	< 0.001	97% (155)***	< 0.001
Corticosteroids	34% (113)	74% (122)***	< 0.001	83% (166)***	< 0.001	94% (151)***	< 0.001
Azathioprine	6% (19)	26% (43)***	< 0.001	28% (56)***	< 0.001	52% (83)***	< 0.001
Methotrexate	18% (60)	52% (86)***	< 0.001	53% (105)***	< 0.001	42% (67)***	0.005
Mycophenolate	5% (18)	19% (31)***	0.003	36% (72)***	< 0.001	41% (65)***	< 0.001
IVIG	8% (28)	42% (69)***	< 0.001	47% (94)***	< 0.001	36% (57)***	< 0.001
Rituximab	0% (0)	24% (40)***	..	17% (33)***	..	24% (38)***	..

Dichotomous variables were expressed as a percentage (count) and continuous variables as mean (SD). Univariate comparisons of continuous variables were made using Student´s t-test while dichotomous variables were compared either using the chi-squared test or Fisher´s exact test, as appropriate. Multivariate comparisons were performed using logistic regression for dichotomous variables. All multivariate comparisons were adjusted by age at onset, sex, race, and duration of follow-up (time from the onset to the last follow-up). IBM: Inclusion body myositis. IMNM: Immune medication necrotizing myositis. DM: Dermatomyositis. AS: Anti-synthetase syndrome. IVIG: Intravenous immunoglobulin.

Supplementary Table 3. Weakness pattern in inclusion body myositis compared to other types of autoimmune myositis at the first JH visit.

	IBM	IMNM	Multivariate p-value	DM	Multivariate p-value	AS	Multivariate p-value
	(n=335)	(n=165)		(n=199)		(n=160)	
Major muscle regions							
Proximal upper extremity weakness	84% (283)	74% (122)**	< 0.001	59% (117)***	< 0.001	39% (63)***	< 0.001
Distal upper extremity weakness	97% (326)	16% (27)***	< 0.001	27% (54)***	< 0.001	14% (22)***	< 0.001
Proximal lower extremity weakness	93% (311)	87% (143)*	0.01	65% (129)***	< 0.001	56% (90)***	< 0.001
Distal lower extremity weakness	61% (203)	7% (12)***	< 0.001	12% (23)***	< 0.001	2% (3)***	< 0.001
Individual muscle group strength †							
Arm abductors	9.2 (1.6)	8.0 (2.0)***	< 0.001	8.4 (2.4)***	< 0.001	9.3 (1.4)	0.2
Elbow flexors	8.9 (1.5)	8.9 (1.7)	0.4	9.1 (1.5)	0.4	9.7 (0.6)***	< 0.001
Elbow extensors	8.1 (1.7)	8.7 (1.7)**	0.01	8.9 (1.6)***	0.007	9.6 (0.9)***	< 0.001
Wrist flexors	8.2 (1.9)	9.8 (0.7)***	< 0.001	9.7 (0.8)***	< 0.001	9.9 (0.4)***	< 0.001
Wrist extensors	9.1 (1.8)	9.8 (0.6)***	0.008	9.7 (1.0)***	0.03	9.9 (0.4)***	0.004
Finger flexors	5.7 (3.0)	9.7 (0.7)***	< 0.001	9.8 (0.6)***	< 0.001	9.8 (0.6)***	< 0.001
Finger extensors	8.8 (1.9)	9.9 (0.4)***	< 0.001	9.7 (1.0)***	< 0.001	9.8 (0.5)***	0.002
Hip flexors	7.7 (2.5)	5.9 (3.1)***	< 0.001	8.1 (2.5)	0.8	8.8 (1.8)***	< 0.001
Hip extensors	9.8 (0.9)	8.9 (2.3)***	0.004	9.5 (1.5)*	0.02	9.8 (0.7)	0.2
Knee flexors	9.2 (1.5)	9.0 (1.8)	0.6	9.8 (0.9)***	0.005	9.9 (0.4)***	0.004
Knee extensors	6.9 (3.0)	9.2 (1.7)***	< 0.001	9.7 (1.0)***	< 0.001	9.8 (0.5)***	< 0.001
Ankle flexors	8.2 (2.6)	9.8 (0.5)***	< 0.001	9.8 (1.0)***	< 0.001	9.9 (0.3)***	< 0.001
Ankle extensors	9.3 (2.0)	9.8 (0.5)*	0.2	9.9 (0.5)***	0.03	10.0 (0.0)**	0.07

Variables were expressed as a mean (SD). Univariate comparisons were compared using Student´s t-test. Multivariate comparisons were performed using linear regression. All multivariate comparisons were adjusted by age at onset, sex, race, and duration of follow-up (time from the onset to the last follow-up). † Kendall scale. IBM: Inclusion body myositis. IMNM: Immune medication necrotizing myositis. DM: Dermatomyositis. AS: Anti-synthetase syndrome.

Supplementary Table 4: IBM initial diagnoses [†]

Initial Diagnosis	% (n)
Inclusion body myositis	48% (153)
Polymyositis	22% (70)
Dermatomyositis	1% (2)
Statin-associated myositis	4% (13)
Unspecified myopathy	13% (41)
Neuropathy	4% (12)
Motor neuron disease	3% (10
Orthopedic disorder	3% (8)
Other	2% (7)

[†] *Initial diagnoses defined by patient self-report or as otherwise noted in the supplemented medical record. IBM: Inclusion body myositis.*

Supplementary Table 5. IBM ancillary studies

Variable	Result (n)
Electrodiagnostic Studies	
Irritability	86% (243)
Myopathic units	93% (259)
Neurogenic units	44% (122)
Mixed units	41% (114)
Sural SNAP < 9 µV	31% (103)
Serologies	
Median CK (IU/L)	426 (230-707)
Anti-NT5C1A (+)	47% (149)
ANA (+)	40% (79)

IBM: Inclusion body myositis. SNAP: Sensory nerve action potential. CK: Creatine kinase. Anti-NT5C1A: Anti-5'nucleotidase, cytosolic 1A. ANA: Antinuclear antibody.