

The idiopathic inflammatory myopathies module of the Rheumatic Diseases Portuguese Register

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Submitted: 24/01/2023

Accepted: 30/05/2023

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as an 'Accepted Article'

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Abstract

Aims: To characterise the idiopathic inflammatory myopathies (IIM) module of the Rheumatic Diseases Portuguese Register (Reuma.pt/myositis) and the patients in its cohort.

Methods: Reuma.pt is a web-based system with standardised patient files gathered in a registry. This was a multicentre open cohort study, including patients registered in Reuma.pt/myositis up to January 2022.

Results: Reuma.pt/myositis was designed to record all relevant data in clinical practice and includes disease-specific diagnosis and classification criteria, clinical manifestations, immunological data, and disease activity scores. Two hundred eighty patients were included, 71.4% female, 89.4% Caucasian, with a median age at diagnosis and disease duration of 48.9 (33.6-59.3) and 5.3 (3.0-9.8) years. Patients were classified as having definite (N=57/118, 48.3%), likely (N=23/118, 19.5%), or possible (N=2/118, 1.7%) IIM by 2017 EULAR/ACR criteria. The most common disease subtypes were dermatomyositis (DM, N=122/280, 43.6%), polymyositis (N=59/280, 21.1%), and myositis in overlap syndromes (N=41/280, 14.6%). The most common symptoms were proximal muscle weakness (N=180/215, 83.7%) and arthralgia (N=127/249, 52.9%), and the most common clinical signs were Gottron's sign (N=75/184, 40.8%) and heliotrope rash (N=101/252, 40.1%). Organ involvement included lung (N=78/230, 33.9%) and heart (N=11/229, 4.8%) involvements. Most patients expressed myositis-specific (MSA, N=158/242, 65.3%) or myositis-associated (MAA, 112/242, 46.3%) antibodies. The most frequent were anti-SSA/SSB (N=70/231, 30.3%), anti-Jo1 (N=56/236, 23.7%), and anti-Mi2 (N=31/212, 14.6%). Most patients had a myopathic pattern on electromyogram (N=101/138, 73.2%), muscle oedema in magnetic resonance (N=33/62, 53.2%), and high CK (N=154/200, 55.0%) and aldolase levels (N=74/135, 54.8%). Cancer was found in 11/127 patients (8.7%), most commonly breast cancer (N=3/11, 27.3%). Most patients with cancer-associated myositis had DM (N=8/11, 72.7%) and expressed MSA (N=6/11) and/or MAA (N=3/11). The most used drugs were glucocorticoids (N=201/280, 71.8%), methotrexate (N=117/280, 41.8%), hydroxychloroquine (N=87/280, 31.1%), azathioprine (N=85/280, 30.4%), and mycophenolate mofetil (N=56/280, 20.0%). At the last follow-up, there was a median MMT8 of 150 (142-150), modified DAS skin of 0 (0-1), global VAS of 10 (0-50) mm, and HAQ of 0.125 (0.000-1.125).

Conclusions: Reuma.pt/myositis adequately captures the main features of inflammatory myopathies' patients, depicting, in this first report, a heterogeneous population with frequent muscle, joint, skin, and lung involvements.

Keywords: Myositis and muscle disease; Quality of life; Muscle; Neoplasia; Epidemiology.

Accepted article

Introduction

Idiopathic inflammatory myopathies (IIM) are a heterogeneous group of disorders in which chronic inflammation of the skeletal muscle, leading to muscle weakness, is a common feature¹. Dysphagia and dysphonia occur often and can be severe, whereas the involvement of respiratory muscles can be fatal¹. Skin manifestations are very common and vary according to the disease subtypes. Interstitial lung disease (ILD) is a common and severe feature associated with most IIM subtypes². Raynaud's phenomenon (RP), arthritis, and fever are also frequent¹. Myocarditis is a rare but potentially severe manifestation¹.

Myositis-specific (MSA) and myositis-associated (MAA) antibodies (Supplementary Table I) are associated with distinct clinical features. They can help identify subsets of IIM in which extra-muscular symptoms might be the presenting or predominant feature, especially when muscle symptoms are mild or absent^{1,3}.

Different clusters within the IIM spectrum have been identified based on muscle involvement, extra-muscular findings, and immunologic aspects. Dermatomyositis (DM) generally includes the classic skin and muscle involvements of IIM. Clinically-amyopathic dermatomyositis (CADM) represents a clinical phenotype with typical DM skin manifestations and may include internal organ involvement but not significant muscle weakness. Patients with typical DM muscle biopsy but without skin involvement are classified as nonspecific myositis (NSM)¹. Anti-synthetase syndrome (ASSD) is characterised by myositis, ILD, mechanic's hand, hiker's feet, and/or arthritis in the presence of an anti-synthetase antibody^{4,5}. Immune-mediated necrotising myopathy (IMNM) is histologically characterised by necrotic muscle fibres and scarce inflammatory cell infiltrates. Muscle involvement can be very severe, but these patients less often have extramuscular involvement. Inclusion body myositis (IBM) is suggested based on three main features: (i) finger flexor or quadriceps weakness, muscle biopsy showing (ii) the presence of rimmed vacuoles, and (iii) endomysial inflammation and invasion of non-necrotic muscle fibres¹. The morbimortality within the IIM spectrum varies greatly according to the disease subtype, timing of diagnosis and treatment.

Even when considered as a group of diseases, IIM are rare⁶. Geographic factors seem to influence its incidence, prevalence, and severity⁶, specifically latitude⁷. However, the Portuguese population of IIM has never been characterised. Therefore, we aimed to present the Rheumatic Diseases Portuguese Register (Reuma.pt) IIM module to the scientific community and characterise the Portuguese IIM cohort.

Patients and Methods

Reuma.pt

Reuma.pt was created in June 2008 and prospectively follows patients with several rheumatic diseases^{8,9} in specific modules^{10,11}, with a Portuguese and an English version. Owned by the Portuguese Society of Rheumatology, Reuma.pt is a web-based system with standardised patient files that includes data regarding clinical and immunological features, disease activity, patient-reported outcomes (PRO), and implemented treatments. Follow-up visits are registered according to clinical practice, and the collected information is gathered in a registry from which data can be extracted. In April 2019, a specific module for IIM was launched (Reuma.pt/myositis). Its main goals were to characterise the Portuguese IIM cohort and get long-term information on the safety and effectiveness of different treatments.

Study design and data collection

This was a multicentre prospective open cohort study. We included patients clinically classified as having IIM by their assisting physician, registered in Reuma.pt/myositis until January 2022. Data was collected by exporting data directly from Reuma.pt/myositis into an anonymised Microsoft Excel document. We requested access to demographic data (age, age at diagnosis, sex), clinical data [date of the first symptom, date of diagnosis, IIM subtype, fulfilment of the 2017 European Alliance of Associations for Rheumatology (EULAR)/ American College of Rheumatology (ACR)¹² and Bohan and Peter^{13,14} classification criteria, disease manifestations, anti-nuclear antibodies (ANA), MSA and MAA status, creatinine kinase (CK), aldolase, myoglobin, aspartate transaminase (AST), alanine transaminase (ALT), or lactate dehydrogenase (LDH) elevation, EMG, muscle MRI or muscle biopsy with myositis evidence, and worst and most recent Manual Muscle Testing of a Subset of Eight Muscles (MMT8)¹⁵, Childhood Myositis Assessment Scale (CMAS)¹⁶, joint count, modified skin disease activity score (DAS)^{17,18}, and patient's visual analogue scales (VAS)], cancer status (type of cancer, date of diagnosis), and treatment data (previous and current).

Data treatment and report

Some variables were created using the extracted variables. The variable creation was pre-defined and expressed in the project protocol.

Some variables that can be noted in more than one menu were cross-checked, namely lung involvement, heart involvement, Gottron's papules and sign, heliotrope rash, oedema, calcinosis, periungual changes, skin ulcers, and Raynaud's phenomenon.

Descriptive statistics were presented as median (interquartile range) for continuous non-normal variables and as absolute and relative frequencies for categorical variables.

Ethical considerations

The study was conducted according to the principles of the Declaration of Helsinki (revised in Fortaleza – 2013)¹⁹ and was approved by the Ethics Committee of *Centro Académico de Medicina de Lisboa* (195/21) and the Reuma.pt National Committee. Reuma.pt was approved by the national board for data protection (Comissão Nacional de Proteção de Dados) and by all the participating centre's ethics committees. This work's databases and all research process steps were fully anonymised. Furthermore, all patients signed the Reuma.pt informed consent.

Results

Reuma.pt/myositis module

Reuma.pt/myositis' homepage lists all IIM patients from the health professional's centre (Supplementary Figure 1). After entering the patient's file, the patient's identification, contact and demographical data, and a list of the registered visits appear (Supplementary Figure 2). Starting or editing a patient's visit leads to the Visit page, where a sidebar is used to navigate the Visit page (Figure 1A). This sidebar has three main menus: (i) General data, (ii) Today's visit, and (iii) Evolution data. The General data menu includes links to the pages containing the patient's identification, labour situation, diagnosis criteria, 2017 EULAR/ACR classification criteria (Figure 1B), cumulative clinical manifestations (Figure 1C), immunological manifestations (Figure 1D), results from complementary exams, comorbidities, and past medication. Today's visit menu includes links to the pages containing the current medication and adverse events, active clinical manifestations (Figure 2A), MMT8 (Figure 2B) and CMAS, joint count (Figure 2C), modified DAS skin, calcinosis and ulcer registration, myositis intention to treat activity index (MITAX, Figure 2D), VAS, health-assessment questionnaire (HAQ), among other PRO. It is also possible to freely write notes and physical examination data and insert exam results. The evolution data menu can build graphics and charts using data registered in consecutive visits. Besides, patients can access a dedicated online area to complete the PRO before each medical visit.

Reuma.pt/myositis cohort

Demographic data and consumption habits

We included 280 patients from 19 different centres, of whom 71.4% were female, with a median age at diagnosis of 48.9 (33.6-59.3) years and disease duration of 5.3 (3.0-9.8) years. Most patients were Caucasian (N=118/280, 89.4%) or had African ancestry (N=13/132, 9.9%). Some patients were former smokers (N=17/118, 14.4%), actively smoking (N=14/118, 11.9%), or regularly drinking alcohol (N=6/111, 5.4%). Eleven patients (N=11/280, 3.9%) died before the data extraction.

Classification criteria and IIM subtypes

Patients were classified as having definite (N=57/118, 48.3%; N=35/224, 15.6%), likely (N=23/118, 19.5%; N=50/224, 22.3%), or possible (N=2/118, 1.7%; N=46/224, 20.5%) IIM by 2017 EULAR/ACR and Bohan-Peter criteria, respectively.

The most common disease subtype was DM (N=122/280, 43.6%), followed by PM (N=59/280, 21.1%), myositis in overlap syndromes (N=41/280, 14.6%), CADM (N=17/280, 6.1%), NSM (N=13/280, 4.6%), mixed connective tissue disease (N=12/280, 4.3%), IMNM (N=9/280, 3.2%), and IBM (N=7/280, 2.5%).

The overlap syndromes included PM/systemic sclerosis (SSc) overlap (N=7), DM/SSc overlap (N=3), PM/systemic lupus erythematosus (SLE) overlap (N=2), and DM/SLE overlap (N=2).

Clinical features

Muscle involvement

Most patients presented proximal muscle weakness (N=180/215, 83.7%). The median last MMT8 was 150 (142-150)/150 (Figure 3). Paediatric IIM patients had a median last CMAS of 53 (53-53)/53. Most patients had high serum muscle enzymes, with a median highest serum CK levels of 1308 (518-3172) mg/dL, aldolase of 42 (12-121) mg/dL, LDH of 549 (414-958) mg/dL, AST of 114 (65-236) mg/dL, and ALT of 109 (56-175) mg/dL. In addition, most patients who had an EMG performed had a myopathic pattern (N=101/138, 73.2%), and most of those who did a muscle MRI had muscle oedema (N=33/62, 53.2%).

Joint involvement

Most patients in our cohort had arthralgia (N=127/249, 52.9%), and more than a third of the patients had arthritis (N=38/98, 38.8%). Almost a tenth of the patients had at least one painful joint in the last registered joint count (N=17/186, 9.1%), but only seven patients had at least five painful joints at the last follow-up (N=7/186, 3.8%, Figure 4). The same seven patients

also had five or more swollen joints at the last follow-up (N=7/186, 3.8%). Only one patient (that had a PM/SSc overlap syndrome) had joint contractures (N=1/82, 1.2%).

Skin involvement

The most common cutaneous manifestation was Gottron's sign (N=75/184, 40.8%), followed by heliotrope rash (N=101/252, 40.1%), Gottron's papules (N=93/237, 39.2%), erythema (N=63/166, 38.0%), periungual changes (N=55/222, 24.8%), malar rash (N=30/131, 22.9%), photosensitivity (N=27/130, 20.8%), and the shawl sign (N=26/130, 20.0%). Mechanic's hands (N=24/130, 18.5%), cutaneous vasculitis (N=26/182, 14.3%), periorbital oedema (N=15/125, 12.0%), and calcinosis (N=24/233, 10.3%) were also present in more than 10% of patients. Other skin involvements were less common but included severe manifestations such as skin ulceration (N=16/230, 7.0%) and generalised subcutaneous oedema (N=6/126, 4.8%). More than a tenth of the patients had a modified DAS skin \geq 3 at the last follow-up (N=19/150, 12.7%) (**Figure 5**). The median last modified Rodnan skin score (mRSS) was 7.5 (0.5-23.5) in patients with SSc overlap syndromes.

Cardiopulmonary and gastrointestinal involvement

Lung involvement occurred in a third of the patients (N=78/230, 33.9%). Dysphagia (N=33/121, 27.3%) and dysphonia (N=12/120, 10.0%) were also prevalent. Heart involvement was less frequent (N=13/230, 5.9%). Some patients complained of abdominal pain (N=5/118, 4.2%) and were diagnosed with gastric (N=2/220, 0.9%) or intestinal involvement (N=3/221, 1.4%).

Vascular involvement

Raynaud's phenomenon was experienced by almost a third of the patients (N=76/234, 32.5%), and periungual capillary changes were also frequent (N=22/115, 19.1%). On the other hand, digital ulcers occurred in a single patient (N=1/107, 0.9%) with a SSc overlap syndrome.

Systemic involvement

Nonspecific symptoms were very prevalent. More than a third of patients experienced fatigue (N=47/127, 37.0%), and weight loss was also common (N=22/127, 17.3%). Fever was only reported by six patients (N=6/128, 4.7%).

Cancer-associated myositis

Cancer was found in 11/127 patients (8.7%), most commonly breast (N=3/11, 27.3%), non-melanoma skin (N=2/11, 18.2%), and colorectal (N=2/11, 18.2%) cancer (**Table I**). Most patients with cancer-associated myositis had DM (N=8/11, 72.7%) and expressed MSA (N=6/11, 54.5%) and/or MAA (N=3/11, 27.3%).

Immunological features

Most patients were seropositive (N=254/280, 90.7%) for MSA (N=158/242, 65.3%) and/or MAA (N=112/242, 46.3%). Notably, less than two-thirds of patients had a positive indirect immunofluorescence assay (IIFA) on HEp-2 cells (N=161/242, 66.5%), i.e., more than a third of the patients were ANA negative.

The most frequent MSA was anti-histidyl tRNA synthetase (anti-Jo1, N=56/236, 23.7%), followed by anti-Mi-2 (N=31/212, 14.6%), anti-signal recognition particle (anti-SRP, N=14/201, 7.0%), anti-melanoma differentiation-associated gene 5 (anti-MDA-5, N=11/199, 5.5%), anti-threonyl tRNA synthetase (anti-PL7, N=10/209, 4.8%), anti-alanyl tRNA synthetase (anti-PL12, N=8/207, 3.9%), anti-small ubiquitin-like modifier activating enzyme (anti-SAE, N=7/198, 3.5%), anti-nuclear matrix protein 2 (anti-NXP2, N=7/198, 3.5%), anti-transcription intermediary factor 1-gamma (anti-TIF1 γ , N=6/200, 3.0%), anti-glycyl tRNA synthetase (anti-EJ, N=4/201, 2.0%), and anti-isoleucyl tRNA synthetase (anti-OJ, N=4/201, 2.0%) antibodies.

The most common MAA were anti-Sjögren's syndrome-related antigen A/B (anti-SSA/SSB, N=70/231, 30.3%), anti-polymyositis/scleroderma (anti-Pm/Scl, N=17/215, 7.9%), anti-ribonucleoprotein (anti-RNP, N=15/227, 6.6%), and anti-Ku (N=10/207, 4.8%) antibodies.

Currently and previously used treatments

The most used drugs were glucocorticoids (N=201/280, 71.8%). The most commonly used disease-modifying antirheumatic drugs (DMARDs) were methotrexate (N=117/280, 41.8%), hydroxychloroquine (N=87/280, 31.1%), azathioprine (N=85/280, 30.4%), mycophenolate mofetil (N=56/280, 20.0%), and cyclophosphamide (N=16/280, 5.7%). The calcineurin inhibitors tacrolimus (N=6/280, 2.1%) and cyclosporine (N=3/280, 1.1%) were not frequently used.

Biologic DMARDs used included rituximab (N=45/280, 16.1%), adalimumab (N=3/280, 1.1%), and infliximab (N=3/280, 1.1%).

Intravenous immunoglobulin was also commonly used (N=55/280, 19.6%).

Patient-reported outcomes

At the last follow-up, there was a median patient global VAS of 10 (0-50) mm and HAQ of 0.125 (0.000-1.125).

Discussion

Reuma.pt/myositis is a valuable electronic clinical record and online registry for IIM patients, designed to record all relevant data in clinical practice following a standardised approach. Reuma.pt/myositis can help improve and homogenise the quality of clinical care to this group of patients. In addition, the data gathered through routine use of Reuma.pt/myositis is extremely valuable for research, especially considering the rarity of the disease and its geographical variations.

This is the first description of Reuma.pt/myositis and its cohort of IIM patients. This work was important to raise awareness about this Reuma.pt module in the Portuguese Rheumatology community, aiming at promoting its use in daily clinical practice and the development of new studies within its framework. Additionally, we hope this paper helps promote Reuma.pt/myositis internationally and its inclusion in IIM registry consortiums.

In this study, we included all patients diagnosed with IIM according to their assisting physician, regardless of whether they met the classification criteria. We believe this is the best way to reflect real-world data, especially considering that all IIM classification criteria are stringent. Nevertheless, most included patients were classified as having definite or likely IIM by the 2017 EULAR/ACR classification criteria.

The sex distribution in Reuma.pt/myositis (71.4% females) was similar to other IIM cohorts, such as Euromyositis²⁰ and the REMICAM registry²¹, and higher than the one reported for the MyoCite cohort²². Our cohort comprises 89.4% Caucasians, a higher ratio than Euromyositis. The median age at diagnosis was also similar to the Euromyositis cohort²⁰ and slightly higher than the REMICAM registry and MyoCite cohort. Considering that Euromyositis and REMICAM are European registries, while MyoCite is an Indian cohort, these differences seem to reflect geographical differences, although we cannot ascertain if these are due to different genetical backgrounds, exposures or both.

The percentage of smokers was lower in Reuma.pt/myositis than Euromyositis. Of note, we did not find recent data concerning alcohol consumption habits in IIM.

The most common IIM subtype was DM, such as in Euromyositis and MyoCite. However, the percentage of patients with DM was slightly higher than in both these cohorts. This difference may be related to the nonexistence of the ASSD subtype as a possible classification in Reuma.pt/myositis, leading to the classification of patients with ASSD as DM and PM. The second most common IIM subtype was PM, similar to the Euromyositis registry. Our 21.1% PM prevalence is an intermediate value between those reported by the MyoCite (11%) and those of Euromyositis (27%) and REMICAM (29%). Myositis as an overlap condition in connective tissue

diseases was our third most common IIM subtype, such as in the Euromyositis and REMICAM cohorts. The 14.6% prevalence in Reuma.pt/myositis is also an intermediate value between those reported by Euromyositis (12%) and those of REMICAM (21%) and MyoCite (27%). IMNM was very rare (3.2%), such as in the Euromyositis cohort (3%). Finally, the prevalence of IBM in our cohort (2.5%) was lower than that of Euromyositis (8%) because IBM patients are generally taken care of by Neurologists in Portugal.

The most common symptoms in our cohort were proximal muscle weakness, arthralgia, fatigue, Raynaud's phenomenon, and dysphagia. The most common clinical signs were Gottron's sign, heliotrope rash, Gottron's papules, and arthritis.

The percentage of patients with muscle weakness (96.6%) was similar to the reported by Euromyositis (93%), MyoCite (93%), and REMICAM (95.5%), and most patients presented proximal muscle weakness, as expected in IIM¹. However, the median worse MMT8 of 146/150 is less severe than the median MMT8 of 73/80 reported in the Euromyositis registry. This discrepancy may be due to the fact that the Reuma.pt/myositis cohort is a prospectively collected cohort rather than an inception cohort, meaning that the first MMT8 score recorded may not be from disease onset. This is also true for other metrics in this paper, such as CMAS, joint count, modified DAS skin, patient global VAS, and HAQ. Nevertheless, a numerical difference is evident between the worse and the last registered MMT8 in our cohort. The prevalence of dysphagia in our cohort (27.3%) is in line with that reported in the REMICAM cohort (26.6%) and is lower than Euromyositis (39%). Dysphagia is a frequent IBM symptom, and the lower ratio of IBM patients in Reuma.pt/myositis and REMICAM may explain this discrepancy.

Arthralgia, a clinical symptom that was not reported in any of the three previously reported IIM cohorts, was reported by most patients in our cohort. Additionally, 38.8% of patients had arthritis, an intermediate percentage between Euromyositis (28%) and REMICAM (42.7%).

Skin involvement was widespread and diverse in the Reuma.pt/myositis cohort. The most common cutaneous manifestations were Gottron's sign, heliotrope rash, Gottron's papules, erythema, periungual changes, malar rash, photosensitivity, and the shawl sign, all classically associated with DM. Typical DM rashes are reported in 54% of patients in the Euromyositis registry and 48.8% of patients in the REMICAM cohort. However, none of the three published IIM cohorts reported the individual prevalence of all the different DM rashes. The Euromyositis paper reports a 33% prevalence of periungual erythema, higher than our reported 24.8%. Mechanic's hands were present in 18.5% of our IIM patients, very similar to the 19% reported on the Euromyositis cohort. Calcinosis was reported in 10.3% of our patients, similar to

REMICAM (10.6%) but not Euromyositis (6%) cohort. Skin ulceration is a severe cutaneous manifestation reported in 7.0% of our cohort, such as in the Euromyositis registry (7%).

Lung involvement is reported in a very similar amount of IIM patients (33.9%) compared to Euromyositis (30%), REMICAM (29.6%), and MyoCite (28%) cohorts. Heart involvement was less frequent in Reuma.pt/myositis (5.9%) than in Euromyositis (9%) and REMICAM (20.1%). It is uncertain if this was due to under-reporting, under-diagnosis, different definitions of heart involvement, or true differences in clinical phenotypes. A third of Reuma.pt/myositis patients experienced Raynaud's phenomenon (32.5%), similar to Euromyositis (34%) and REMICAM (28.6%) cohorts. Fatigue was common in our cohort (37.0%), although it was not reported by any of the three published IIM cohorts.

Adult patients with IIM are at increased risk for cancer^{23,24}. The relationship between cancer and myositis has been known for several years now and keeps challenging clinicians and researchers alike. An important definition is that of cancer-associated myositis, which comprises the onset of cancer within three years of an IIM diagnosis²⁵. In this study, we only considered cancer-associated myositis. In our cohort, we found a prevalence of cancer-associated myositis of 8.7%, similar to the one reported in REMICAM (8.3%) but higher than Euromyositis (5%) and MyoCite (2%). However, the total number of patients with a history of cancer was 13% and 15% in Euromyositis and REMICAM, respectively. Breast cancer was the first cause of cancer-associated myositis in our cohort, similar to Euromyositis. However, despite being frequent, it was only the fourth most common type of cancer in the REMICAM cohort. In REMICAM, the tumours most frequently involved were lung and skin cancer and lymphoma. On the other hand, Euromyositis reports bowel, ovarian, and lung cancers as the second, third and fourth most common types of cancer, respectively. As expected, most patients with cancer-associated myositis in our cohort had DM (72.7%), as DM is clearly associated with an increased risk of cancer compared to other IIM subtypes^{20,24,26}.

Most patients in our cohort expressed MSA (65.3%) and/or MAA (46.3%), substantially more than the patients in the MyoCite cohort (38% for MSA and 19.6% for MAA, respectively). Consequently, the percentage of seronegative IIM patients was much lower in Reuma.pt/myositis (9.3%) than the MyoCite cohort (40.8%). A number of causes may explain these differences. First, given the availability of the immunoblots, there may be a higher reliance on immunological testing for assuming the diagnosis of IIM in Portugal, but it is also possible that there is some overdiagnosis in the MyoCite cohort. On the other hand, different testing methods and inter-rater differences using the same tests may also highly influence the results of the immunological testing. Lastly, seronegative IIM may be more frequent in India or autoantibodies that are more prevalent in Asia than in Europe may still not have been

discovered. On the contrary, more patients in the MyoCite cohort (76%) had a positive IIFA on HEp-2 cells than in Reuma.pt/myositis (66.5%). Just like in our cohort, anti-Jo1 (23.7%) was the most frequent MSA in REMICAM (16.8%) and the MyoCite cohort (8%), followed by anti-Mi2 (14.6% in Reuma.pt/myositis, 12.6% in REMICAM, and 7% in MyoCite). No other MSA reached a prevalence of over 10% in any of the cohorts. The most common MAA in our cohort was anti-SSA/SSB (30.3%). This number is probably an overestimate of the prevalence of anti-Ro52. The most significant current limitation of Reuma.pt/myositis is that anti-SSA/SSB antibodies are coded in the same variable. This means we cannot distinguish anti-Ro52, anti-Ro60, and anti-La antibodies using Reuma.pt, which is an issue, especially considering the importance of anti-Ro52 ILD risk assessment in IIM patients²⁷. This issue has already been reported and is currently under review. Nevertheless, anti-Ro52 is also the most common MAA in the MyoCite cohort (13%), followed by anti-Pm/Scl (4%), such as in Reuma.pt/myositis (7.9%).

The British Society for Rheumatology (BSR) guideline on the management of paediatric, adolescent and adult patients with IIM, published in 2022, highlighted the limited high-quality evidence available to support treatment decisions, with a relative absence of randomised controlled trials or head-to-head comparison of treatments²⁸. For that reason, recommendations were predominantly based on observational studies. Given the rarity of IIM, registry-based observational studies performed in platforms like Reuma.pt/myositis can significantly improve the knowledge about the management and treatment of IIM. Off-label use of immunomodulators is frequent in clinical practice, as is shown by Reuma.pt/myositis data. The most used drugs in our cohort were glucocorticoids (71.8% of patients), such as in the Euromyositis (98%) and REMICAM (98.9%) cohorts. However, the proportion of patients who did not have glucocorticoid use registered in our cohort was much higher than in the other two cohorts. Although some patients, such as the IBM, IMNM or some myositis/SSc overlap patients, may have been treated without the use of glucocorticoids, this proportion is highly suggestive of under-reporting. The fact that Reuma.pt/myositis is not an inception cohort may contribute to this under-reporting of glucocorticoid use since patients may not have been under glucocorticoids when they were included in Reuma.pt/myositis. The most commonly used DMARD was methotrexate (41.8%), just like in REMICAM (47.7%) and Euromyositis (71%). This is coherent with the BSR guidelines, which indicate methotrexate as a first-line treatment of myositis in both children and adults²⁸. The second most used DMARD in Reuma.pt/myositis was hydroxychloroquine (31.1%), more often used than in the Euromyositis (25%) and REMICAM (16.1%) cohorts, in which it was only the fourth most used DMARD. The extensive use of hydroxychloroquine in our cohort may be due to the high prevalence of DM and its cutaneous manifestations, for which hydroxychloroquine can be used as an off-label treatment²⁹. Another

likely cause for the use of hydroxychloroquine is the high prevalence of arthralgia and arthritis in Reuma.pt/myositis cohort³⁰. Finally, it could also reflect the local prescription patterns preferences, considering that other drugs, such as azathioprine, were used less in our cohort compared to international cohorts. Despite its lower usage than in other countries (51% of patients in the Euromyositis registry and 39.6% of patients in the REMICAM cohort), azathioprine was still the third most used DMARD in our cohort (in 30.4% of patients). The most commonly used biologic DMARD was rituximab (16.1%). Despite the apparent greater use of rituximab compared to the Euromyositis (7%) and REMICAM (9.4%) cohorts, we must consider that the reports about these cohorts were published in 2018 and 2017, respectively, when rituximab was probably less accessible.

The data recording on Reuma.pt/myositis is completely voluntary. This could lead to missing data issues. While we encountered missing data in our analysis, particularly in the treatment data and prospective disease activity scores, overall, the data was robust and consistent with our expectations.

Reuma.pt/myositis comprises a group of various subtypes of IIM with different clinical manifestations. Although the data gathered is still insufficient to compare these different groups of IIM patients effectively or study them extensively in isolation, the structured information will keep adding up and may be merged with information from other registries. From a research point of view, the ultimate goal will be to achieve a bigger data set with statistical power to allow for clinically meaningful research on the registry data.

Conclusions

Reuma.pt/myositis is an efficient tool to systematically evaluate IIM patients and expand our current knowledge on this group of diseases. In this first report, Reuma.pt/myositis adequately captures the main features of IIM patients, depicting a heterogeneous population with frequent muscle, joint, skin, and lung involvements. Demographic, clinical, and immunological features of Portuguese IIM patients are generally similar to those of other populations. Arthralgia and fatigue, whose prevalences were not previously described, were very frequent in our IIM cohort.

Tables and Figures

Table I - Autoantibodies and IIM subtypes in cancer-associated myositis

Cancer	IIM subtypes	Autoantibodies
Breast	DM (3)	Mi2, SRP (+ SSA/SSB), Pm/Scl
Skin (non-melanoma)	Clinically amyopathic DM, PM	Jo1, SAE (+SSA/SSB)
Colorectal	DM (2)	Mi2 (2)
Kidney	DM	-
Lung	DM	-
Lymphoma	Inclusion bodies myopathy	-
Unknown	DM	-

DM – dermatomyositis; IIM – idiopathic inflammatory myopathies; Jo1 – anti-histidyl-tRNA synthetase antibodies; Mi2 – anti-Mi-2 antibodies; PM – polymyositis; Pm/Scl – anti-polymyositis/scleroderma antibodies; SAE – anti-small ubiquitin-like modifier activating enzyme antibodies; SRP – anti-signal recognition particle antibodies; SSA/SSB – anti-Sjögren's syndrome-related antigen A/B antibodies.

Supplementary Table I

Supplementary Table I - Myositis-specific and myositis-associated antibodies.

Myositis-specific anti-synthetase antibodies	Myositis-specific antibodies (other than anti-synthetase)	Myositis-associated antibodies
Anti-Jo1	Anti-SRP	Anti-Pm/Scl
Anti-PL7	Anti-HMGCR	Anti-RNP
Anti-PL12	Anti-Mi-2	Anti-Ku
Anti-EJ	Anti-MDA5	Anti-Ro52
Anti-OJ	Anti-TIF1γ	Anti-mitochondrial antibody
Anti-Zo	Anti-NPX2	
Anti-YRS/Ha	Anti-SAE	
Anti-KS	Anti-CN1A	

anti-CN1A – anti-cytosolic 5'-nucleotidase 1A antibodies; anti-EJ – anti-glycyl tRNA synthetase antibodies; anti-HMGCR – anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase antibodies; anti-Jo1 – anti-histidyl tRNA synthetase antibodies; anti-KS – anti-asparaginyl-transfer tRNA synthetase antibodies; anti-MDA5 – anti-melanoma differentiation-associated gene 5 antibodies; anti-NPX2 – anti-nuclear matrix protein 2; anti-OJ – anti-isoleucyl tRNA synthetase antibodies; anti-PL7 – anti-threonyl tRNA synthetase antibodies; anti-PL12 – anti-alanyl tRNA synthetase antibodies; anti-Pm/Scl – anti-polymyositis/scleroderma antibodies; anti-RNP – anti-ribonucleoprotein antibodies; anti-SAE – anti-small ubiquitin-like modifier activating enzyme antibodies; anti-SRP – anti-signal recognition particle antibodies; anti-TIF1γ – anti-transcription intermediary factor 1-gamma antibodies; anti-YRS/Ha – anti-tyrosyl tRNA synthetase antibodies; anti-Zo – anti-phenylalanyl tRNA synthetase antibodies.

Supplementary Figure 1

Protocol: Myositis [Exportar para ficheiro] [New patient]

Number of patients: 128 (34 males and 94 females)

Sit. Seq.	Patient ID	Process	Name	Birth date	bDMARD/tsDMARD
Edit					
Edit					
Edit					
Edit					
Edit					
Edit					
Edit					
Edit					
Edit					
Edit					
Edit					
Edit					
Edit					
Edit					
Edit					

Filters Name [] Process Nr. [] Patient ID []

Press the <ENTER> key after fill in the search data.

Supplementary Figure 1 – Reuma.pt/myositis starting page. This page displays a table with all IIM patients from the health professional’s centre. Also, it is also possible to check if the patients on the list are under any bDMARD or tsDMARD treatments. Data that could identify the patient’s identity was removed from the figure.

Supplementary Figure 2

Centre: User: Eduardo Dourado

Patient data

Main diagnosis: Myositis [Share with another Centre]

DB internal No. []

Patient Record No. []

Patient Card No. []

Name []

Surname []

Birthdate [] [] []

Sex: Male Female

Email []

Profile: Select a profile []

Access to the patient's area [Instructions for accessing the patient's area]

Yes, with access to the information recorded by the doctor (password must be provided)

Yes, without access to the information recorded by the doctor

No, without access to the patient's area

[Save] [Delete]

Visits [Delete or modify dates] [New visit]

Most recent visits at the top of the list

Sit.	Diag.	Date	Doctor
Edit	Myo		
Edit	Myo		
Edit	Myo		
Edit	Myo		
Edit	Myo		
Edit	Myo		
Edit	Myo		
Edit	Myo		
Edit	Myo		
Edit	Myo		
Edit	Myo		

Supplementary Figure 2 – Patient’s file in the Reuma.pt/myositis module. Identification, contact, and demographical data appear on the upper left. The patient’s research profile and which data is being displayed in the Patient’s Area appears on the down left. Finally, a list of the patient’s registered visits appears on the right. Data that could identify the patient’s identity was removed from the figure.

Figure 1

General data

- Identification
- Clinical situation
- Labor situation
- Diagnosis criteria
- Classification Crit. 2017
- General clinical data/Manif.
- Immunological manifestations
- Diagnostic complementary exams
- Alcohol / Tobacco
- Associated Conditions
- Neoplasms

Past Medication

- Rheumatic
- Other Medication
- Surgeries
- Procedures
- Non-pharmacological Treatm.

Today's visit

- >Notes / Plan
- Associated conditions<

Disease assessment

- Joints
- VAS
- HAQ

Additional questionnaires

- MMT8
- Skin evaluation
- Calcinosis
- Ulcers
- Clinical features
- MITAX
- EQ5D
- HADS
- SF36
- FACIT
- WPAl
- IPAQ

Complementary exams

- Lab results
- GI involvement
- Imaging
- Physical Examination

Vaccines and tuberculosis

Drugs and Adverse events

- Medications
- Adverse events
- Visit report

Evolution data

- Graphic Evolution
- Chart Evolution

EULAR/ACR Criteria 2017 - Diagnosis of polymyositis and dermatomyositis

Age of onset of first symptom: [0 - 17] [18 - 39] [40+] [yyyy] [mm] [dd]

Fraqueza simétrica objetiva, geralmente progressiva, das extremidades superiores proximais: [No] [Yes] [UNK/ND] [yyyy] [mm] [dd]

Objective symmetric weakness, usually progressive, of the proximal lower extremities: [No] [Yes] [UNK/ND] [yyyy] [mm] [dd]

Neck flexors are relatively weaker than neck extensors: [No] [Yes] [UNK/ND] [yyyy] [mm] [dd]

In the legs proximal muscles are relatively weaker than distal muscles: [No] [Yes] [UNK/ND] [yyyy] [mm] [dd]

Hellotrope rash: [No] [Yes] [UNK/ND] [yyyy] [mm] [dd]

Gottron's papules: [No] [Yes] [UNK/ND] [yyyy] [mm] [dd]

Gottron's sign: [No] [Yes] [UNK/ND] [yyyy] [mm] [dd]

Dysphagia or esophageal dysmotility: [No] [Yes] [UNK/ND] [yyyy] [mm] [dd]

Anti-Jo-1 (anti-Histidyl-tRNA synthetase) autoantibody positivity: [No] [Yes] [UNK/ND] [yyyy] [mm] [dd]

Elevated serum levels of creatine kinase (CK) or lactate dehydrogenase (LDH) or aspartate aminotransferase (ASAT/AST/SGOT) or alanine aminotransferase (ALAT/ALT/SGPT): [No] [Yes] [UNK/ND] [yyyy] [mm] [dd]

Endomyosial infiltration of mononuclear cells surrounding, but not invading, myofibers: [No] [Yes] [UNK/ND] [yyyy] [mm] [dd]

Perimysial and/or perivascular infiltration of mononuclear cells: [No] [Yes] [UNK/ND] [yyyy] [mm] [dd]

Perifascicular atrophy: [No] [Yes] [UNK/ND] [yyyy] [mm] [dd]

Rimmed vacuoles: [No] [Yes] [UNK/ND] [yyyy] [mm] [dd]

Classification: [] Score: []
Probability: [] Subgroup: []

CLINICAL MANIFESTATIONS

Myositis

Onset of symptoms: [yyyy] [mm] [dd] Diagnosis date: [yyyy] [mm] [dd] Rheumatologist: []

Notes: []

Mark all manifestations as No

	No	Yes	UNK/ND	Beginning date
Myositis	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	[yyyy] [mm] [dd]
Gottrons Papules	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	[yyyy] [mm] [dd]
Helliotrope Rash	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	[yyyy] [mm] [dd]
Raynaud's phenomenon	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	[yyyy] [mm] [dd]
Ulceration	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	[yyyy] [mm] [dd]
Oedema	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	[yyyy] [mm] [dd]
Calcinosis	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	[yyyy] [mm] [dd]
Nailfold Changes	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	[yyyy] [mm] [dd]
Lipatrophy	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	[yyyy] [mm] [dd]
Arthralgia/arthritis	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	[yyyy] [mm] [dd]
Esophageal involvement	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	[yyyy] [mm] [dd]
Gastric involvement	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	[yyyy] [mm] [dd]
Intestinal involvement	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	[yyyy] [mm] [dd]
Cardiac involvement	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	[yyyy] [mm] [dd]
Pulmonary involvement	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	[yyyy] [mm] [dd]
Other	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	[yyyy] [mm] [dd]

Specify: []

Immunological manifestations

Mark all manifestations as No

Immunological manifestations	No	Yes	Unknown
Antinuclear antibodies (ANA)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Anti-Mi2	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Anti-TIF1γ	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Anti-MDA5	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Anti-NXP2	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Anti-SAE1	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Anti-Ku	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Anti-PM-Scl	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Anti-SRP	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Anti-PI-7	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Anti-PL-12	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Anti-EJ	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Anti-OJ	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Anti-RNP	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Anti-SSA/SSB	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Anti-Jo1	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Others	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Figure 1 – Visit page in the Reuma.pt/myositis module (General data). A sidebar is used to navigate the Visit page (panel A). This sidebar has three main menus: (i) General data, (ii) Today's visit, and (iii) Evolution data. The General data menu includes links to the pages containing the patient's identification, labour situation, diagnosis criteria, 2017 EULAR/ACR classification criteria (panel B),

cumulative clinical manifestations (panel C), immunological manifestations (panel D), results from complementary exams, comorbidities, and past medication.

Figure 2

The image displays a complex digital form for myositis assessment, divided into four main panels:

- Panel A: Clinical features and Kendall Manual Muscle Testing (MMT8).** This section includes a checklist of clinical manifestations such as proximal muscle weakness, active skin diseases (like heliotrope rash and Gottron's papules), and major organ involvement (musculoskeletal, gastrointestinal, pulmonary, cardiac). Below this is the Kendall MMT8 section, which allows for manual muscle testing on the left and right sides of the body, listing muscles like Neck Flexors, Shoulder Abductors, and Hip Extensors. It includes a 'Total/80' and 'Total/150' score calculation and a 'Save' button.
- Panel B: Joint count diagrams.** Three anatomical diagrams of the human body are shown, labeled 'Tender joints', 'Swollen joints', and 'Reduced mobility joints'. Each diagram has checkboxes to indicate the presence or absence of these joint conditions.
- Panel C: MITAX (Muscle Involvement Test for Assessment of Xeroderma).** This panel contains several horizontal scales for different disease activity domains: Constitutional Disease Activity, Cutaneous Disease Activity, Systemic Disease Activity, Gastrointestinal Disease Activity, Pulmonary Disease Activity, and Cardiovascular Disease Activity. Each scale has a 'Mark all as normal' checkbox and a 'Maximum' score indicator.
- Panel D: Immunological and other disease activity.** This panel includes sections for 'Immunological Disease Activity' and 'Other Disease Activity', with similar horizontal scales and checkboxes for evaluation.

Figure 2 – Visit page in the Reuma.pt/myositis module (Today's visit). Today's visit menu includes links to the pages containing the active clinical manifestations (panel A), MMT8 (panel B), joint count (panel C), and MITAX (panel D).

Figure 3

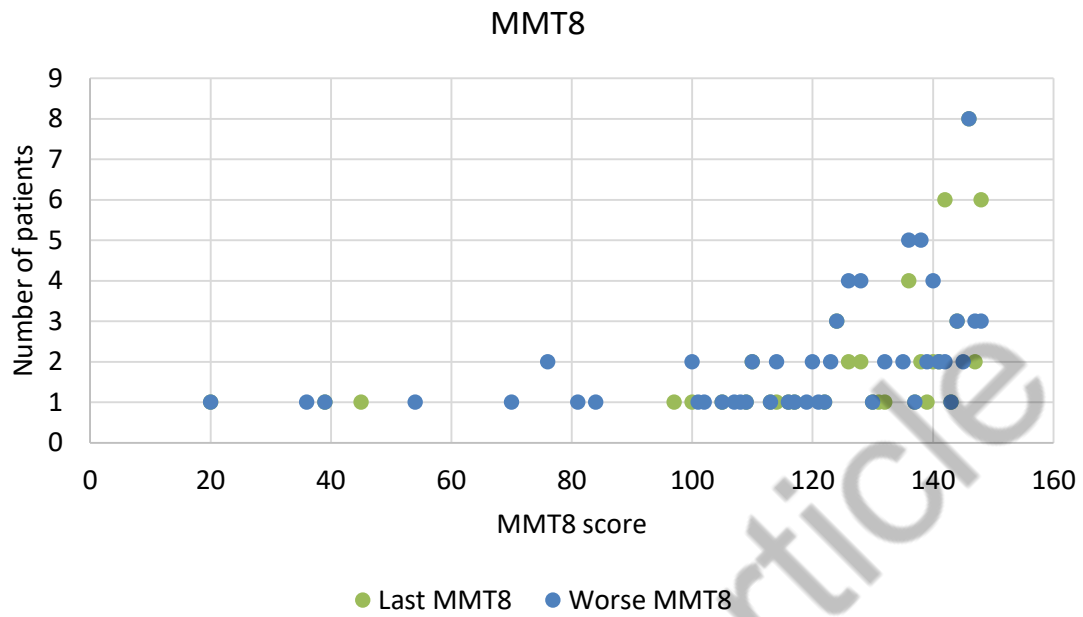


Figure 3 - Worse and last registered MMT8 for each individual patient in the Reuma.pt/myositis cohort. For the sake of readability, the MMT8=150 are not shown.

Figure 4

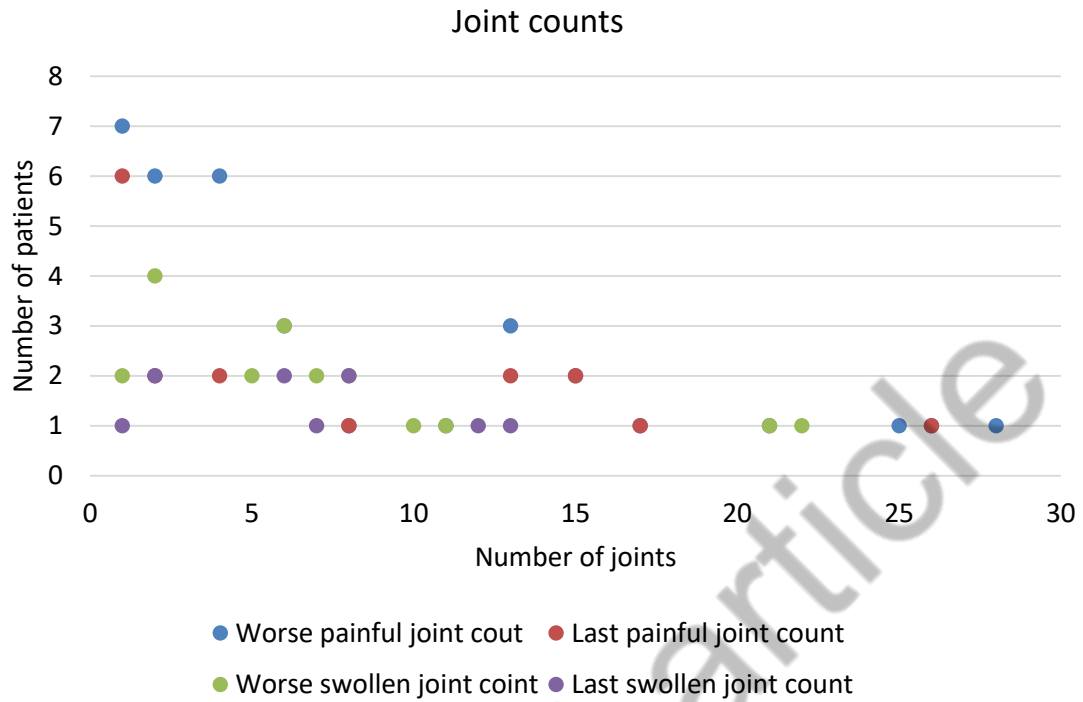


Figure 4 - Worse and last registered joint counts for each individual patient in the Reuma.pt/myositis cohort. For the sake of readability, the joint counts=0 are not shown.

Figure 5

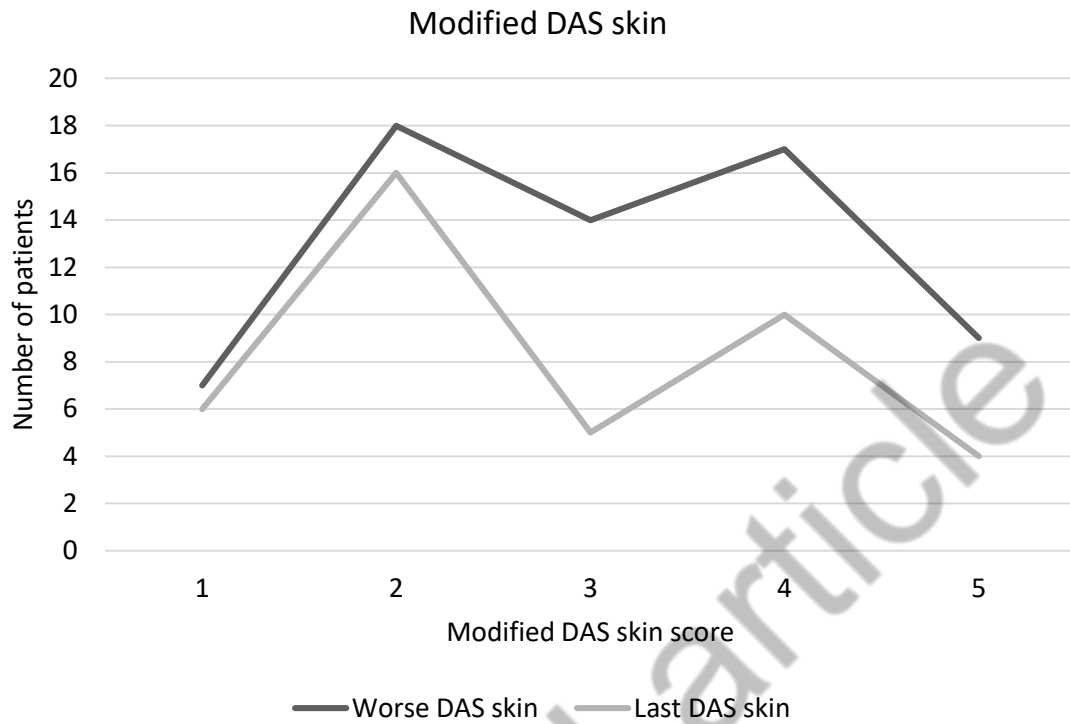


Figure 5 - Worse and last registered modified DAS skin for each individual patient in the Reuma.pt/myositis cohort. For the sake of readability, the modified DAS skin=0 are not shown.

Accepted article

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