Autoimmunity Reviews 22 (2023) 103353

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

A machine learning analysis to evaluate the outcome measures in inflammatory myopathies

Maria Giovanna Danieli [a,b,*], Alberto Paladini [c], Eleonora Longhi [d], Alessandro Tonacci [e,1], Sebastiano Gangemi [f,1]

[a] SOS Immunologia delle Malattie Rare e dei Trapianti, AOU delle Marche & Dipartimento di Scienze Cliniche e Molecolari, Università Politecnica delle Marche, via Tronto 10/A, 60126 Torrette di Ancona, Italy
[b] Postgraduate School of Allergy and Clinical Immunology, Università Politecnica delle Marche, via Tronto 10/A, 60126 Ancona, Italy
[c] Postgraduate School of Internal Medicine, Università Politecnica delle Marche, via Tronto 10/A, 60126 Ancona, Italy
[d] Scuola di Medicina e Chirurgia, Alma Mater Studiorum, Università degli Studi di Bologna, 40126 Bologna, Italy
[e] Institute of Clinical Physiology, National Research Council of Italy (IFC-CNR), Via G. Moruzzi 1, 56124 Pisa, Italy
[f] Operative Unit of Allergy and Clinical Immunology, Department of Clinical and Experimental Medicine, University of Messina, Via Consolare Valeria 1, 98125 Messina, Italy

ARTICLE INFO

Keywords:
Anti-synthetase syndrome
Dermatomyositis
Immune-mediated necrotizing myositis
Machine learning
Multi-omics
Outcome
Polymyositis

ABSTRACT

Objective: To assess the long-term outcome in patients with Idiopathic Inflammatory Myopathies (IIM), focusing on damage and activity disease indexes using artificial intelligence (AI).
Background: IIM are a group of rare diseases characterized by involvement of different organs in addition to the musculoskeletal. Machine Learning analyses large amounts of information, using different algorithms, decision-making processes and self-learning neural networks.
Methods: We evaluate the long-term outcome of 103 patients with IIM, diagnosed on 2017 EULAR/ACR criteria. We considered different parameters, including clinical manifestations and organ involvement, number and type of treatments, serum creatine kinase levels, muscle strength (MMT8 score), disease activity (MITAX score), disability (HAQ-DI score), disease damage (MDI score), and physician and patient global assessment (PGA). The data collected were analysed, applying, with R, supervised ML algorithms such as lasso, ridge, elastic net, classification, and regression trees (CART), random forest and support vector machines (SVM) to find the factors that best predict disease outcome.
Results and conclusion: Using artificial intelligence algorithms we identified the parameters that best correlate with the disease outcome in IIM. The best result was on MMT8 at follow-up, predicted by a CART regression tree algorithm. MITAX was predicted based on clinical features such as the presence of RP-ILD and skin involvement. A good predictive capacity was also demonstrated on damage scores: MDI and HAQ-DI.
In the future Machine Learning will allow us to identify the strengths or weaknesses of the composite disease activity and damage scores, to validate new criteria or to implement classification criteria.

1. Introduction

Idiopathic inflammatory myopathies (IIM) are a group of lifelong immune-mediated disorders characterized by inflammation of skeletal muscle with involvement of other organ systems [1]. Dermatomyositis (DM), polymyositis (PM), immune-mediated necrotizing myositis (IMNM), a- hypomyopathic dermatomyositis, juvenile dermatomyositis (JDM), and inclusion body myositis (IBM) are the subtypes identified by

Abbreviations: ASS, Anti-synthetase syndrome; DL, Deep Learning; DM, Dermatomyositis; HAQ-DI, Health Assessment Questionnaire- Disability Index; IMNM, immune-mediated necrotizing myositis; MDI, Myositis Damage Index; MITAX, Myositis Intention To Treat Activity Index; ML, Machine learning; MMT8, Manual Muscle Testing-8; PM, Polymyositis.

* Corresponding author at: Clinica Medica, Dipartimento di Scienze Cliniche e Molecolari, Via Tronto 10A, Torrette di Ancona 60126, Italy.
E-mail addresses: m.g.danieli@univpm.it (M.G. Danieli), albertopaladini1@gmail.com (A. Paladini), eleonora.longhi@studio.unibo.it (E. Longhi), atonacci@ifc.cnr.it (A. Tonacci), sebastiano.gangemi@unime.it (S. Gangemi).
[1] Both Authors contributed equally to the study.

https://doi.org/10.1016/j.autrev.2023.103353
Received 7 April 2023; Accepted 29 April 2023
Available online 2 May 2023

the 2017 EULAR/ACR classification criteria [2,3]. Added to these major subtypes there is anti-synthetase syndrome (ASS) [4].

Diagnosis is guided by the clinical manifestations and serum creatine kinase elevation on laboratory tests, characteristic EMG findings, presence of myositis-specific or associated antibodies [5]. In addition, muscle MRI and biopsy may be helpful.

The severity of the disease is closely related to the clinical phenotype: the prognosis is often influenced by the presence of underlying neoplasm, mainly associated with anti-TIF1-gamma and anti-NXP-2 antibodies. Interstitial lung disease (ILD) most often accompanies ASS and anti-MDA5-positive ADM and negatively influences the prognosis in rapidly progressive forms (RP-ILD) [1,6].

Treatment is based on immunosuppressants, primarily steroids and other steroid-sparing agents such as methotrexate, azathioprine, mycophenolate mofetil, and rituximab [1,5]. A good response with reduced immunosuppressive effects has been demonstrated with the use of high-dose intravenous immunoglobulin (IVIg) and subcutaneous Ig (SCIg) in selected cases [7–9].

In previous works Artificial Intelligence (AI) has already applied in the field of medicine [10,11] and in myositis [12–15]. In this study we are going to analyze by artificial intelligence the parameters that influence the course and especially the outcome of our patients with myositis.

2. Patients and methods

2.1. Patient population

Our series comprised 103 adult consecutive in- and out- patients with new-onset myositis, diagnosed, treated and prospectively followed in the Clinica Medica of the Marche Polytechnic University and AOU delle Marche, a tertiary referral Centre in Italy. All patients, including those previously diagnosed with the Bohan & Peter's classification criteria [16] for definite myositis, met the 2017 EULAR/ACR classification criteria for myositis [2]. The presence of an anti-synthetase antibody and concomitant myositis, interstitial lung disease (ILD), mechanics' hands, Raynaud's phenomenon, arthritis, and fever lead to the diagnosis of anti-synthetase syndrome (ASS) [4]. Immune mediated necrotizing myopathy (IMNM) was diagnosed by the clinical pictures of myositis associated with a positive test of antibodies against signal recognition particle (anti-SRP) or against 3-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR) [17]. Patients with inclusion body and juvenile myositis were not included in this study.

2.2. Clinical evaluation

Demographic, clinical, serologic, and radiologic data, and treatment modalities were collected during follow-up visits using a standardized protocol. We included patients with diagnoses made before October 31st, 2020, to obtain a follow-up lasting $\geq$2 years. We included patients who died before a two-year follow-up due to myositis-related complications.

Each patient was evaluated at the first visit and thereafter every 6 months or when clinically indicated. The visit included a general physical examination and muscle strength assessment by manual 8-muscle test (MMT-8, 0 to 80) [18].

As laboratory tests, we evaluated creatine kinase (CK, with normal values <170 U/l).

Nerve conduction and concentric needle EMG studies were made in line with standard techniques. At the onset of the disease, expert pathologists evaluated muscle biopsy specimens with light and electron microscopies.

Myositis-specific and myositis-associated serum autoantibodies were searched by immunoblotting (Alphadia, Belgium). Since this testing is accessible in our hospital just from 2015, 80% patients performed these tests. Other immunological parameters consisted of antinuclear antibodies (ANA); anti-double stranded (ds)- DNA antibodies; anti-extractable nuclear antigen (ENA) antibodies with immunoblotting analysis to identify different patterns.

All patients were screened for underlying malignancy.

Organ systems involvement was managed together with referring specialists.

Skin involvement and its severity were assessed in all patients, using the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) in 48% of DM patients (diagnosed and/or followed-up from 2010) [18].

The gastrointestinal tract was evaluated by dysphagia tests to assess esophageal motility, using the Dysphagia Outcome and Severity Scale, a 7-point scale from 1 (severe dysphagia) to 7 (normal in all situations), as a benchmark [19].

Pulmonary function and the possible presence of ILD were assessed by tests of respiratory function and lung diffusion capacity to carbon monoxide and high-resolution computed tomography.

Cardiac involvement was assessed by cardiological examination and echocardiography, with global longitudinal strain (GLS) [20].

Major events and causes of death were established by a death certificate.

The disease course was defined as monocyclic, polycyclic, or chronic continuous according to the definitions of Marie et al. [21].

2.3. Myositis indexes

2.3.1. Assessment of disease activity

Disease activity is defined as potentially reversible and related only to the myositis disease process. To evaluate this topic, we employed the Myositis Intention to Treat Activities Index (MITAX) [21]. Briefly, MITAX explores the disease activity in seven organ systems, comprising constitutional, cutaneous, skeletal, gastrointestinal, pulmonary, cardiac and muscle. Each clinical manifestation is calculated according to the degree of inflammatory activity, from 0 (not present) to 4 (new feature). The summed component scores lead to a global score, which is divided by the maximum possible score. MITAX score ranged from 0 (no activity) to 1 (severe activity).

2.3.2. Assessment of damage

The MDI score was used to evaluate persistent changes in 11 scales, collectively termed organ systems, including muscular, skeletal, cutaneous, gastrointestinal, pulmonary, cardiovascular, peripheral vascular, endocrine, and ocular involvement, plus infections and malignancies [18]. Each scale comprises 2–8 items scored as present (if persisting for at least 6 months) or absent. The presence or absence of each item was summed to provide a total MDI extent of damage score (potential range 0–38 in adults). To obtain MDI values comparable to each other, the total MDI of each patient was normalized for the number of items considered for the single patient. MDI score ranged from 0 (no damage) to 1 (damage).

2.3.3. Assessment of disability

The disability scale of the Health Assessment Questionnaire (HAQ-DI) evaluates the physical function. This comprises 20 questions investigating eight activities: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and other activities [18]. The HAQ-DI is graded from zero (no difficulty) to 3 (unable to do). To estimate the HAQ-DI, the highest sub-category score determines the value for each category, unless aids or devices are used; responses in at least six of the eight categories are necessary to calculate the HAQ-DI. The HAQ-DI is then computed dividing the summed component scores by the number of components answered. Disability was classified as moderate to severe with a HAQ-DI score $\geq$ 1.0 [18].

All clinical evaluations of patients, completed by the above indices, were performed by expert clinicians (MGD, AP) who were trained in the use of the instruments and their definitions.

2.4. Treatment

We collected the data related to treatment and side effects in a dedicated form. Treatments employed included:

Glucocorticoids: oral prednisone (PDN) at high doses at 1 mg/kg/day for 4–6 weeks and then slowly reduced to an average of 0.25 mg/kg every other day or high-dose intravenous methylprednisolone (10–15 mg/kg in three consecutive daily boluses then switching to 1 mg/kg/day).

Steroid-sparing agents / immunosuppressants: azathioprine (AZA) at 1–1.5 mg/kg/day; cyclosporine A (CSA) at an initial oral dose of 3 mg/kg/day for six months, later reduced to a maintenance dose of 2 mg/kg/day; mycophenolate mofetil (MMF) titrated slowly to an oral dose of 2 g/day; methotrexate (MTX) with a subcutaneous dose of 10–15 mg/week; rituximab (RTX) with two intravenous infusions of 1 g two weeks apart, that can be repeat after 6–9 months. Intravenous cyclophosphamide was used in boluses of 750–1000 mg monthly for six months. Hydroxychloroquine at 200 mg/day after the initial dosage of 400 mg/day for one month.

Immunomodulatory therapy: intravenous immunoglobulin (IVIg) at high dose of 2 g/kg divided into five consecutive days each month for six months, followed by three additional bimonthly cycles; subcutaneous immunoglobulin 20% (20%SCIg, Hizentra®, CSL Behring GmbH, Marburg) with treatment dose was 0.1–0.2 g/kg, once a week on the same day. The drug was administered with a Super-PID Crono PCa-50 programmable pump (Canè S.R.L. Turin, Italy). Patients treated with SCIg before 2011 started with 16%SCIg (Vivaglobin®, CSL Behring GmbH, Marburg, Germany) and then changed to SCIg 20%. Treatment with SCIg occurred in two ways: consequentially after 6 months of therapy with IVIg 2 g/kg in patients with severe disease; in combination with PDN in patients with newly diagnosed moderate disease or in case of relapse.

2.5. Informed consent

We obtained approval from the Ethic Committee of Marche Region (CERM) (Prot. Number 20122024 Affari Generali AOU Ospedali Riuniti; CERM Protocol 2021 485, December 16th, 2021). Each patient was formally informed about modalities and aims of the study and informed consent was obtained. The study was performed in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki.

3. Machine Learning: general principles

3.1. Introduction to machine learning

Machine learning (ML) was applied to predict several clinical outcomes of the patients included in the dataset given the input data collected by the clinical staff involved in the present study. Such clinical outcomes include: i) HAQ-DI, ii) MDI, iii) MITAX, iv) MMT8, v) amount of immunosuppressors. For such investigations, it is required that the ML models perform an estimation of a correct value as output, minimizing as much as possible the error (generally, the Root Mean Squared Error, RMSE) between the real and the predicted value. Under such premises, the task demanded is represented by a regression task.

For all the outcomes, a best solution is sought, in terms of the RMSE minimization, with respect to several models, as explained shortly after. Overall, the dataset was divided into 80% of data used for training the models (training set) and 20% for model performances evaluation (test set). The models were tested with a 10-fold cross-validation to reduce overfitting, trying to cope with the model generalizability on new data [22,23].

From the original dataset, for each of the analysis performed, a variable selection was first carried out, with the application of a General Linear Model (GLM), with whom all the variables with a p-value below $p = 0.10$, were checked for multicollinearity, and then selected for use in the respective prediction model.

Overall, the ML analysis was carried out under the open-source R language, using the software RStudio, version 2022.12.0 Build 353 for Windows, available with the GNU Affero General Public License. All the models were run on a laptop equipped with AMD Ryzen 53,500 U with Radeon Vega Mobile Gfx at 2.10 GHz.

3.2. Machine learning models

For the present study, six different supervised models (given the a priori knowledge of the output values) suitable for regression purposes were implemented and employed to predict the outcomes. Such models included Least Absolute Shrinkage and Selection Operator (LASSO), RIDGE regression, Elastic Net, Classification and Regression Trees (CART), Random Forest (RF) and Support Vector Machines (SVM). All such models are shortly presented below.

3.2.1. Least absolute shrinkage and selection operator (LASSO)

The Least Absolute Shrinkage and Selection Operator, worldwide known as the LASSO, is a popular ML model, used for regression purposes. It includes both variable selection and regularization, aiming at improving the prediction accuracy and the resulting model interpretability. Simple to implement and quite fast, it is deemed particularly useful in presence of several variables hypothesized not being useful for prediction [24].

3.2.2. RIDGE regression (RIDGE)

Also popular like the LASSO, Ridge Regression is often employed with multicollinear data. In such cases, least squares estimates are totally unbiased, with a large variance, deviating them significantly from their true value. By adding a given bias to the regression estimates, RIDGE reduces the standard errors, shrinking all the variables' coefficients to a non-zero value [25].

3.2.3. Elastic net

The Elastic Net merges together the characteristics of both LASSO and RIDGE, blending them. Its main regularization parameter can be fine-tuned between 0 and 1, with the lower boundary making the model equal to RIDGE and the upper limit to LASSO [26].

3.2.4. Classification and regression trees (CART)

Classification and Regression Trees (CART) are commonly used, powerful ML models. They deconstruct the whole dataset into smaller groups, via binary splits of the sample, repeated one variable at a time. CART features speed of execution, adaptation to nearly all kinds of data (cross sectional, longitudinal, survival data), without requiring to be distributed in a Gaussian fashion. At the same time, CART can be used both for classification and regression problems. On the other hand, they are quite sensitive to small data changes, also presenting a limited interpretability [27].

3.2.5. Random Forest

Random Forest (RF) are very popular ML models, that can be applied to both regression and classification tasks. Like CART, they also rely on decision trees for training, but in a much higher amount, making up a “forest” of trees. Similarly to CART, they do not need any particular data preparation prior to the application of the model. In addition, they perform implicit on-the-run feature selection and provide more accurate indicators of feature importance. Moreover, they are unlikely to perform overfitting, they are relatively quick to train and versatile, however their interpretability is questionable [28].

3.2.6. Support vector machines (SVM)

Support Vector Machines (SVM) are robust, commonly used methods for prediction, for both classification and regression purposes. When

receiving a set of training observations, with a labelled category, SVM builds a model assigning new observations to a category or to another, mapping the training observations to points into the space, trying to maximize the gap between the categories. New observations presented are then mapped and predicted based on the side of the gap they fall to. To perform this task, different kinds of classification can be applied, including linear (the most popular and simplest one), or non-linear ones, mapping inputs into high-dimensional feature spaces, with the use of dedicated kernels (radial, polynomial, sigmoid, etc). For the present study, to manage the trade-off between prediction accuracy, computational load and execution speed, we evaluated the performances of linear and radial basis function (RBF) kernels [29].

4. Results

4.1. Main patients' characteristics

Our series included 103 patients with myositis: PM ($n = 33$), DM ($n = 53$), ASS ($n = 9$), and IMNM ($n = 8$). Tables 1 and 2 show their baseline characteristics at the time of diagnosis, the treatment modalities and response to treatment. The mean follow-up was 10 years (range 1–28 ys; median 9.6 ys).

Nineteen patients (11F, median age 57 years) had several types of cancer. The most frequent were breast ($n = 4$), lymphoma (n = 3), lung and colon ($n = 2$, each).

Thirty-three patients (16F/17M, mean age 64 ± 15, median 67 years) died after a mean follow-up f 10 years (median 7 years). Main causes of death were neoplasia ($n = 10$), ILD (n = 10), cardiomyopathy ($n = 7$). Among these, a 45-year-old man with severe-onset DM died, while in remission, for acute myocardial ischemia in COVID-19 interstitial pneumonia.

4.2. Prediction of activity at last follow-up visit (MITAX score)

In our series, age- and sex-adjusted mean MITAX values at the diagnosis of inflammatory myopathies was 0.21 ± 0.15 (median 0.2, range 0.05–0.5). At the end of follow-up, we still detected high MITAX scores (0.20 ± 0.10, median 0.19, range 0.05–0.5) in the whole population, in particular in patients with heart and lung involvement.

With the ML, the first prediction was related to the MITAX score at the follow-up. As displayed in Table 3, the linear SVM outperformed all the other models, making best use of 17 support vectors, and featuring a mean error below 7% (6.9%) with respect to the average output value.

Concerning the predictors, the presence of Rapidly Progressive Interstitial Lung Disease (RP-ILD) at baseline, together with the presence of skin involvement, seems to give the best predictive value for MITAX.

Table 1
Baseline characteristics of our series of 103 patients with inflammatory myopathies.

	n	%
Age at diagnosis (years), median (min–max)	53 (18–86)	
Gender: Females	76	73
Type of myositis		
PM	33	34
DM	53	49
ASS	9	8
IMNM	8	7.7
Autoantibodies positivity: (negative in 20 pts)		
Antinuclear antibodies	21	20
Anti-SRP	6	4.8
Anti-HMGCR	2	1.9
Anti-Jo1	8	7.7
Anti-Mi-2	5	4.8
Anti-TIF1	3	2.9
Anti-MDA-5	2	1.9
Anti-EJ, NXP2 (each)	3	2.9
Anti-myositis-associated autoantibodies (SSA, SSB, RNP, etc)	23	22.3
Organ involvement		
Interstitial lung disease	42	40.7
Clinically overt heart involvement	28	27.1
Dysphagia	59	57.2
Arthritis	33	32.0
Course of disease		
Monocyclic	28	27.1
Polycyclic	27	26.2
Chronic continuous	48	46.6
Mean follow-up period (min–max) (From treatment start to the last visit; years)	10 (1–28)	

Table 2
Treatment modalities and response to treatment in our series of 103 patients with inflammatory myopathies.

	n	%
Treatment modalities		
Oral prednisone / methylprednisolone	103	100
Hydroxychloroquine	10	9.7
Immunosuppressant (AZA, CsA, CYC, MMF, MTX)	79	76.6
Rituximab	7	6.7
Tocilizumab	4	3.8
IVIg treatment	21	20
Synchronized IVIg-20%SCIg treatment	22	21
Direct 20%SCIg treatment	8	7.7
Skeletal muscle response		
Complete response	45	43.6
Partial response	40	38.8
Non responder	18	17.4
Mean follow-up period (min–max) (From treatment start to the last visit; years)	10 (1–28)	

AZA: Azathioprine; CsA: Cyclosporin A; CYC: Cyclophosphamide; MMF: Mycophenolate mofetil; MTX: Methotrexate.
IVIg: Intravenous Immunoglobulin; 20%SCIg: Subcutaneous Immunoglobulin

4.3. Prediction of damage at last follow-up visit (MDI index)

At the end of the follow-up period, the mean MDI score was 0.16 ± 0.14 (median 0.12) with damage present in 83/103 (80%) of the whole population. The mean MDI values showed a constant increase during the years, as confirmed by the median values obtained at 3-, 5- and 10 years (data not shown - 0.07; 0.11 and 0.16; respectively). The most frequent items recorded in our patients were muscle atrophy, muscle dysfunction and muscle weakness (data not shown).

The second ML outcome computed is related to the prediction of the MDI score at the follow-up. For such prediction, the RMSE values, along with the related hyperparameters, are displayed in Table 4.

The best performance overall was achieved again by the SVM, this time with the application of the RBF kernel, outperforming the other models in terms of error (RMSE) minimization. Such performance was achieved in a relatively short amount of time (the model employed just 18.7 s to be trained and provide results), making it usable in nearly any use scenario. The SVM model with the RBF kernel made best use of 69 support vectors, and returned an excellent performance, being its mean error around 5% of the average value of the outcome (more specifically, the 5.16%).

When it comes to the variable importance, overall, it seems that the variables with the highest prediction towards the MDI at follow-up include: the MITAX score, the HAQ-DI at the first visit and the age of the patient at the diagnosis.

4.4. Prediction of disability at last follow-up visit (HAQ-DI score)

In the whole series, the mean HAQ-DI score values at the last evaluation were 1.04 ± 0.86 (median 0.8; range 0–3), with eleven (10%) patients having no disability, and 22 (21%) patients having moderate to severe disability.

The third ML assessment was related to the prediction of the HAQ-DI

Table 3
Performances on the test set of the different models in predicting the MITAX score at follow-up.

	LASSO	RIDGE	ELASTIC NET	CART	RF	SVM	
						LINEAR	RBF
RMSE	0.311	0.917	0.231	0.183	0.408	0.114	0.182
Hyperparameter(s)	$\alpha = 0.1$	$\lambda = 0.1$	$\alpha = 0.05$, $\lambda = 0.1$	cp = 0.037	mtry = 2	cost = 0.001	cost = 1, $\gamma = 0.1$

Table 4
Performances on the test set of the different models in predicting the MDI score at follow-up.

	LASSO	RIDGE	ELASTIC NET	CART	RF	SVM	
						LINEAR	RBF
RMSE	0.070	0.080	0.069	0.107	0.086	0.067	0.064
Hyperparameter (s)	$\alpha = 0.1$	$\lambda = 0.1$	$\alpha = 0.05$, $\lambda = 0.1$	cp = 0.078	mtry = 2	cost = 0.1	cost = 1, $\gamma = 0.01$

score at the follow-up. For this task, performances of the different models are displayed in Table 5.

In this analysis, the SVM resulted to be the best performing model, using a linear kernel, simple and fast to train (the response was provided in just under 10 s). 7.39% was the percentage of the mean error of the SVM model with respect to the average value of the outcome variable, making the prediction enough accurate. Overall, the linear SVM performing at best employed 74 support vectors, and the input variables, which were more predictive for the outcome, resulted to be the health status at the last control and the MDI score at the baseline.

4.5. Prediction of muscle strength at last follow-up visit (MMT8 score)

The fourth outcome estimation was concerning the MMT8 at follow-up (range 43–80, mean value: 73). Results obtained by the different models are displayed in Table 6.

In this analysis, the CART was the best performing model, with an excellent performance (the mean error being just 0.6% than the mean value of the outcome variable). The overall CART tree is depicted in Fig. 1.

The prediction of the MMT8 at follow-up makes its best using the value of the MMT8 score at baseline, followed by the MITAX score achieved at baseline, too, representing the two most predictive variables for the outcome. The algorithm reported a sequential binary choice starting from the MMT8 at the baseline with a threshold of around 68 (index-linked 0.74). Patients with higher MMT8 (32%) had a mean MMT8 values at last follow-up visit around 79. For patients with a lower MMT8 score (< 68), it was necessary to assess the baseline MITAX: if MITAX score was $\geq$0.32 (index-linked 0.67) the final mean MMT8 score was 65 (in 23% of patients). On the contrary, if the pre MITAX was $<$0.32, the ML evaluated again the pre MMT8 score with a lower threshold of around 58 (index-linked 0.55): if the value was higher the final mean MMT8 was 74 (32% of patients), if lower the final mean MMT8 was 67 (in 13% of patients).

4.6. Immunosuppressant use

The fifth and final prediction was related to the number of immunosuppressors displayed, ranging 0–5 (Table 7).

In this final analysis, Random Forest performed at best, with a 10.5% mean error with respect to the average value of the outcome variable. As for the most predictive parameters for the outcome, these resulted to be the CPK value at baseline and the number of immunosuppressors at the first evaluation (the number of immunosuppressant therapies changed). As displayed in Fig. 2, the optimal value of the error was already reached with around 300 trees (the actual analysis was performed with 500), so that the elapsed time (summing up to 20 s for the current scenario) could be eventually further decreased without significantly affecting the results.

Overall, the performances of the best models in predicting the different outcomes are reported in Table 8, whereas Table 9 present a summary of the data obtained by Machine Learning analysis.

5. Discussion

In this study, we described our experience about the usefulness of machine learning to predict the clinical outcome in a large group of Italian patients with inflammatory myopathies diagnosed and followed over 10 years in a tertiary care University Hospital centre. Evaluation parameters employed in this study included the MMT8 to estimate the skeletal muscle strength; the MITAX score, exploring the activity of the disease; MDI, a specific index for damage and the HAQ-DI to evaluate disability. Finally, we investigated the predictive parameters linked to the use of immunosuppressants.

When we started studying our cohort of myositis patients, we use the set of criteria of Bohan & Peter [16] for the diagnosis of definite PM and DM. In this study we reviewed our cases accordingly to the new EULAR / ACR classification criteria [2]. With ad hoc protocol, we ruled out the main dystrophic, infectious, toxic, metabolic, or endocrine conditions triggering myopathies. Main demographic, clinical, laboratory and instrumental features of our patients were not different from what previously reported [3,30,31].

The MITAX is a composite score that combines evaluation of seven different organ systems to assess the disease activity. In our series, the mean MITAX value at diagnosis was 0.21 $\pm$ 0.15 (median 0.2), while at follow-up the mean MITAX was 0.20 $\pm$ 0.10, slightly lower. We documented increased MITAX values in patients with DM. At the end of the follow-up, 41% of the whole series still had a slightly increase in MITAX values ($\geq$0.25) indicating an active disease. Globally, patients with ILD, heart involvement and arthritis had higher MITAX values.

Machine learning analysis using SVM model demonstrated the ability to predict MITAX at follow-up with an error of about 7%, in which

Table 5
Performances on the test set of the different models in predicting the HAQ-DI score at follow-up.

	LASSO	RIDGE	ELASTIC NET	CART	RF	SVM	
						LINEAR	RBF
RMSE	0.805	0.692	0.794	0.725	0.749	0.658	1.054
Hyperparameter (s)	$\alpha = 0.229$	$\lambda = 0.1$	$\alpha = 0.261$, $\lambda = 0.042$	cp = 0.268	mtry = 2	cost = 0.1	cost = 10, $\gamma = 0.05$

Table 6
Performances on the test set of the different models in predicting the MMT8 score at follow-up.

	LASSO	RIDGE	ELASTIC NET	CART	RF	SVM	
						LINEAR	RBF
RMSE	5.634	6.553	5.649	5.410	5.648	5.859	6.237
Hyperparameter (s)	$\alpha = 0.447$	$\lambda = 0.1$	$\alpha = 0.472$, $\lambda = 0.018$	cp = 0.061	mtry = 3	cost = 100	cost = 1, $\gamma = 0.05$

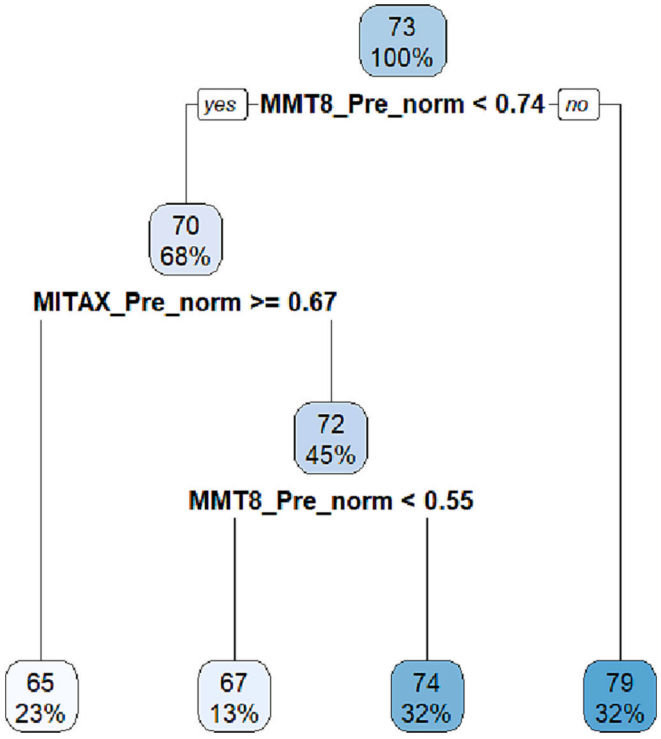

Fig. 1. CART for predicting the MMT8 score at follow-up.

the main predictors are represented by the presence of rapidly progressive interstitial lung disease (RP-ILD) and the cutaneous involvement. We considered RP-ILD as the worsening in pulmonary function developed between 6 weeks and 6 months, or the onset of acute respiratory failure (ARDS) with radiological evidence of ILD. RP-ILD is an interesting aspect in the course of the disease. Our patients with RP-ILD had aggressive disease at onset, often with exclusive pulmonary involvement and with diagnostic delay due to admission to the ICU for ARDS. In addition, lung damage in these patients represents a substrate favoring consequent infectious episodes. In our series only four patients presented RP-ILD of which one had ASS specific antibodies anti-Jo1, one presented anti-MDA5, one had anti-NXP-2 and the last had negative serology; two of them died before the minimum follow-up time (2 years). In the literature, very variable survival rates are described in cases involving patients with RP-ILD, ranging from a 27% survival rate at 3 years [32], up to 73% survival at 5 years [33], in accordance with this finding the survival in our cohort is 50%. Machine learning analysis reported a strict correlation between patients with RP-ILD and higher MITAX at follow-up. However, since two patients died due to respiratory failure as a complication of myositis in the absence of a complete remission, this could have impacted on the final MITAX score.

Another factor related to MITAX at final follow-up is skin involvement. To the best of our knowledge, in literature similar data are not reported on adult myositis: skin involvement often is refractory to therapies [34] but is not significantly related to disease activity. Concerning cases of Juvenile DM, multiple evidence has been reported between skin and higher disease activity. Van Dijkhuizen et al. [35] reported that cutaneous symptoms assessed through physician global activity score were correlated to higher serum CK values, implying the association with muscle disease. Furthermore, the relapses of skin signs may reflect ongoing systemic disease activity [35]. The refractoriness and lack of complete resolution of the skin involvement in patients with DM could explain because patients with skin involvement have higher systemic disease activity at follow-up.

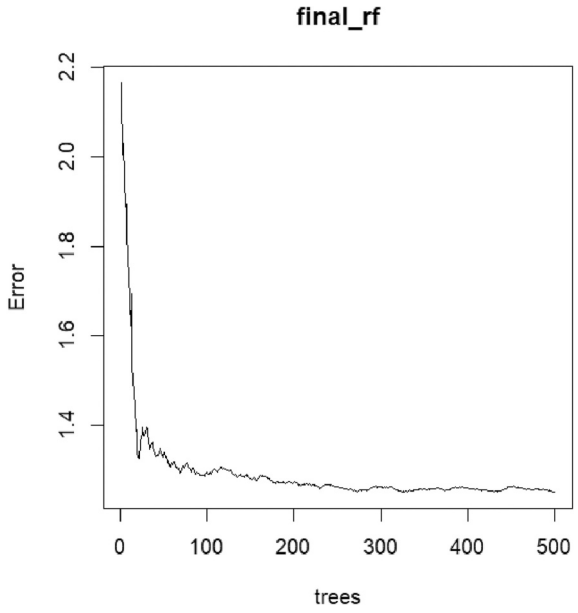

Fig. 2. Error distribution on the training set based on the number of trees composing the Random Forest algorithm in predicting the number of immunosuppressors at follow-up.

Table 8
Performances of the best models in predicting the different outcomes as the percentage error with respect to the mean outcome value.

Outcome	MITAX score	MDI index	HAQ-DI score	MMT8 score	Immunosuppressant use
% Error	6.9%	5.16%	7.39%	0.6%	10.5%

Table 7
Performances on the test set of the different models in predicting the number of immunosuppressors present at follow-up.

	LASSO	RIDGE	ELASTIC NET	CART	RF	SVM	
						LINEAR	RBF
RMSE	0.917	0.922	0.918	0.915	0.894	0.992	0.930
Hyperparameter (s)	$\alpha = 0.423$	$\lambda = 0.1$	$\alpha = 0.472$, $\lambda = 0.1$	cp = 0.249	mtry = 2	cost = 5	cost = 10, $\gamma = 0.05$

Table 9
Summary of the data obtained by Machine Learning analysis.

Predicted follow-up indexes		Machine Learning model Analysis	First most predictive variable	Second most predictive variable	Third most predictive variable
ACTIVITY INDEX	MITAX	Linear SVM	RP-ILD at the onset	Skin involvement	
	MMT8	CART	MMT8 baseline	MITAX baseline	MMT8 baseline
DAMAGE INDEX	MDI	RBF SVM	MITAX baseline	HAQ-DI baseline	Age at the diagnosis
	HAQ-DI	Linear SVM	Health status at last visit	MDI baseline	

HAQ-DI: Health Assessment Questionnaire- Disability Index; MDI: Myositis Damage Index; MITAX: Myositis Intention To Treat Activity Index; MMT8: Manual Muscle Testing-8.

The Myositis Damage Index (MDI) is a composite score that evaluates overall disease damage. In our cohort, MDI was higher in male and in patients with a diagnostic delay longer than six months and a chronic continuous disease course, thus confirming previous reports [3,36]. We found that damage was most frequently present in the muscular and articular systems and even though not statistically significant we documented a tendency towards higher MDI values in patients with heart or esophageal involvement (data not shown).

The machine learning analysis, using the SVM model and an error margin of about 5%, report as predictive factors of the MDI value at follow-up the MITAX score and the HAQ-DI at the first visit, and the age of the patient at the time of diagnosis. The relationship between MDI and the baseline MITAX score could be explained in several ways. An elevated MITAX value could indicate severe disease activity at onset, as well as a diagnostic delay resulting in increased activity due to delayed treatment. Similarly, HAQ-DI score and therefore the initial disability level could equally depend on the late diagnosis and treatment on a more severe disease. Age at diagnosis could be related to MDI at follow-up because younger patients have a better chance of recovery, especially regarding muscle damage.

Rider et al. [36] documented that severity at disease onset, duration of active disease, physician-assessed global disease activity, and adult disability were among the predictors of injury. In a study on juvenile DM population the MDI score, number of organ systems affected, calcinosis, and persistent muscle dysfunction correlated with disease duration, assumed that longer disease activity correlates with greater damage. Also in this study, patients over 7.4 years of age were found to have a greater risk of developing major damage [37].

HAQ-DI is a widely used index which assesses physical function related to activities of daily living, comprising different domains. Gained values $\geq$1.0 denotes a moderate to severe disability [18,38]. According to our analysis, the best performing ML model for HAQ-DI is SVM, which documented as the health status at the last control and the MDI score at the baseline were more predictive for HAQ-DI higher score. Quite all our patients presented a certain degree of disability, with no differences among the different myositis subtypes. Disability associated with a polycyclic or a chronic-continuous course of the disease and the presence of lung involvement. Our data are in line with previous reports [21,39]. In The EuroMyositis registry, Lilleker et al. [30] reported similar HAQ-DI value, with higher score in patients with IBM compared with other myositis subtypes. A significant correlation was found by Vincze et al. [40] among HAQ-DI and the occurrence of vertebral fractures, mostly in the early phases of the disease. Therefore, despite the important progress in treatment, inflammatory myopathies remain a severe disease, which significantly affects the quality of life of patients and their work situation [41].

Finally, we evaluated by machine learning MMT8 which reflects muscular strength and is related to the skeletal disease activity. In this analysis, the CART model predicted with a good performance the MMT8 at the follow-up. The variables with higher prediction towards MMT8 at last follow-up visit are the MMT8 and MITAX values at the baseline.

To our knowledge, this report is the first algorithm capable of estimating MMT8 after an average follow-up of 10 years. Obviously, from a clinical point of view, the data is strictly dependent on the kind of myositis and the treatments used. In a population of patients like ours, very broad and including PM, DM, ASS and IMNM, it could be considered a reference to have a greater awareness of the possible course of the disease. Rider et al. [42] reported a relation between MMT8 and physician's global activity score and HAQ-DI scores and with laboratory parameters such as serum LDH and CK levels.

In a recent study on factors associated with treatment response in inflammatory myopathies subtypes, the presence of higher MMT8 values at baseline and at follow-up was described in patients with anti-SSA antibodies, with better response after treatment [43]. In another study MMT8 was related to daily physical activity and clinical status [44].

In our work machine learning showed good results in predicting disease activity indexes, to a lesser extent on those of damage. The best result, with the least margin of error, was obtained on the prediction of MMT8. The MMT8 represents a more direct and linear index of muscle strength and disease activity, while the MITAX and MDI are composite indices. In our analysis we have considered only some of the existing validated scores to evaluate activity, damage, or improvement in patients with myositis. The reason is to be found because all the scores are not easy to use and feasible in clinical practice, as they require time and qualified personnel, therefore we considered the most long-lived scores applied in more patients.

Aggarwal et al. [45] presented the total improvement score (TIS), a validated composite index, which evaluates the improvement and response to treatment in adult PM/DM. The TIS score includes different core set measures of activity with a different weight on the result and the most important index is represented by MMT8, followed by MITAX and physician global activity score. A limitation of the TIS is represented by its complexity and by its uselessness in identifying disease remission, disease recurrence or the difference between no change and worsening [46].

The difficulty in identifying validated and objective scores that can be used every day, which can be universal and can evaluate the different aspects of the disease, depends on the complexity and variability of organ involvement and severity of the myositis. In this context, a further limitation of our study could be represented by the indistinct series of myositis: in recent years, different pathogenesis, clinical characteristics, severity, and prognosis of the subtypes of myositis emerged, so it could be useful an analysis to better characterize each single subtype. On the other hand, such a large and variable cohort, in consideration of the rarity of the disease, reflects the real patient population.

Machine learning has proven to be useful and reliable in predicting myositis indices, especially in MMT8 which perhaps represents the most significant score with greater weight from a clinical point of view. Its applications could be broader and more comprehensive, even in identifying strengths or weaknesses of each individual disease score, or to improve classification criteria yet described [15,47].

In conclusion, in this paper, we investigated the usefulness of machine learning in predicting the outcome of myositis patients by the means of specific scores. One critical point linked to the use of some of these scores such as MDI and MITAX is that physicians should be skilled to ascribe a modification in a clinical or laboratory feature to a myositis activity/damage, thus excluding other possible causes of the variation of a given parameter and thus differentiating well between activity and damage. Moreover, if the physician is not accustomed with the patient, a longer time is necessary to perform a complete medical history and physical examination. However, despite these limitations, in our hands MITAX and MDI were useful measures of disease activity and damage, respectively, allowing a complete evaluation of muscular and

extramuscular involvement in myositis patients and helping in the therapeutic choice.

MGD and SG were responsible for the study's conception and design. AP and EL made the data acquisition. AT performed the machine learning analyses. All Authors contributed to data interpretation. MGD, AP and SG drafted the manuscript. MGD, AT and SG revised the manuscript critically for intellectual content. All authors gave their final approval of the version of the manuscript to be published.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability

Data will be made available on request.

References

[1] Dalakas MC. Inflammatory muscle diseases. N Engl J Med 2015;372(18):1734–47. https://doi.org/10.1056/NEJMra1402225.

[2] Lundberg IE, Tjärnlund A, Bottai M, International Myositis Classification Criteria Project Consortium, the Euromyositis Register, and the Juvenile Dermatomyositis Cohort Biomarker Study and Repository (UK and Ireland), et al. European league against rheumatism/American College of Rheumatology Classification Criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. Arthritis Rheum 2017;69:2271-82. Ann Rheum Dis 2017;76:1955–64. https://doi.org/10.1136/annrheumdis-2017-211468.

[3] Lundberg IE, de Visser M, Werth VP. Classification of myositis. Nat Rev Rheumatol 2018;14(5):269–78. https://doi.org/10.1038/nrrheum.2018.41.

[4] Zanframundo G, Faghihi-Kashani S, Scirè CA, et al. Defining anti-synthetase syndrome: a systematic literature review. Clin Exp Rheumatol 2022;40(2):309–19. https://doi.org/10.55563/clinexprheumatol/8xj0b9.

[5] Dalakas MC. Inflammatory myopathies: update on diagnosis, pathogenesis and therapies, and COVID-19-related implications. Acta Myol 2020;39(4):289–301. https://doi.org/10.36185/2532-1900-032.

[6] Damoiseaux J, Vulsteke JB, Tseng CW, et al. Autoantibodies in idiopathic inflammatory myopathies: clinical associations and laboratory evaluation by mono- and multispecific immunoassays. Autoimmun Rev 2019;18(3):293–305. https://doi.org/10.1016/j.autrev.2018.10.004.

[7] Danieli MG, Pettinari L, Moretti R, Logullo F, Gabrielli A. Subcutaneous immunoglobulin in polymyositis and dermatomyositis: a novel application. Autoimmun Rev 2011;10(3):144–9. https://doi.org/10.1016/j.autrev.2010.09.004.

[8] Goswami RP, Haldar SN, Chatterjee M, et al. Efficacy and safety of intravenous and subcutaneous immunoglobulin therapy in idiopathic inflammatory myopathy: a systematic review and meta-analysis. Autoimmun Rev 2022;21(2):102997. https://doi.org/10.1016/j.autrev.2021.102997.

[9] Danieli MG, Tonacci A, Paladini A, et al. A machine learning analysis to predict the response to intravenous and subcutaneous immunoglobulin in inflammatory myopathies. A proposal for a future multi-omics approach in autoimmune diseases. Autoimmun Rev 2022;21(6):103105. https://doi.org/10.1016/j.autrev.2022.103105.

[10] Allegra A, Tonacci A, Sciaccotta R, et al. Machine learning and deep learning applications in multiple myeloma: diagnosis, prognosis, and treatment selection. Cancers (Basel) 2022;14(3):606. https://doi.org/10.3390/cancers14030606.

[11] Murdaca G, Caprioli S, Tonacci A, et al. A machine learning application to predict early lung involvement in scleroderma: a feasibility evaluation. Diagnostics (Basel) 2021;11(10):1880. https://doi.org/10.3390/diagnostics11101880.

[12] Zhang W, Huang G, Zheng K, et al. Application of logistic regression and machine learning methods for idiopathic inflammatory myopathies malignancy prediction. Clin Exp Rheumatol 2023;41(2):330–9. https://doi.org/10.55563/clinexprheumatol/8ievtq.

[13] Xue Y, Zhang J, Li C, et al. Machine learning for screening and predicting the risk of anti-MDA5 antibody in juvenile dermatomyositis children. Front Immunol 2023;13:940802. https://doi.org/10.3389/fimmu.2022.940802.

[14] Conrad K, Shoenfeld Y, Fritzler MJ. Precision health: a pragmatic approach to understanding and addressing key factors in autoimmune diseases. Autoimmun Rev 2020;19(5):102508. https://doi.org/10.1016/j.autrev.2020.102508.

[15] Lilleker JB, Chinoy H. Can machine learning unravel the complex IIM spectrum? Nat Rev Rheumatol 2020;16(6):299–300. https://doi.org/10.1038/s41584-020-0412-6.

[16] Bohan A, Peter JB. Polymyositis and dermatomyositis. N Engl J Med 1975;292(7):344. https://doi.org/10.1056/NEJM197502132920706 (403–7).

[17] Musset L, Allenbach Y, Benveniste O, et al. Anti-HMGCR antibodies as a biomarker for immune-mediated necrotizing myopathies: a history of statins and experience from a large international multi-center study. Autoimmun Rev 2016;15:983–93. https://doi.org/10.1016/j.autrev.2016.07.023.

[18] Rider LG, Werth VP, Huber AM, et al. Measures of adult and juvenile dermatomyositis, polymyositis, and inclusion body myositis: physician and patient/parent global activity, manual muscle testing (MMT), health assessment questionnaire (HAQ)/childhood health assessment questionnaire (C-HAQ), childhood Myo-sitisAssessment scale (CMAS), myositis disease activity assessment tool (MDAAT), disease activity score (DAS), short form 36 (SF-36), child health questionnaire (CHQ), physician global damage, myositis damage index (MDI), quantitative muscle testing (QMT), myositis functional Index-2 (FI-2), myositis activities profile (MAP), inclusion body myositis functional rating scale (IBMFRS), cutaneous dermatomyositis disease area and severity index (CDASI), cutaneous assessment tool (CAT), dermatomyositis skin severity index (DSSI), Skindex, and dermatology life quality index (DLQI). Arthritis Care Res (Hoboken) 2011;63 (Suppl. 11):S118–57. https://doi.org/10.1002/acr.20532.

[19] O'Neil KH, Purdy M, Falk J, Gallo L. The dysphagia outcome and severity scale. Dysphagia 1999;14(3):139.

[20] Guerra F, Gelardi C, Capucci A, Gabrielli A, Danieli MG. Subclinical cardiac dysfunction in polymyositis and dermatomyositis: a speckle-tracking case-control study. J Rheumatol 2017;44(6):815–21. https://doi.org/10.3899/jrheum.161311.-45.

[21] Marie I, Hachulla E, Hatron PY, et al. Polymyositis and dermatomyositis: short term and long-term outcome, and predictive factors of prognosis. J Rheumatol 2001;28:2230–7.

[22] Hastie T, Tibshirani R, Friedman J. The elements of statistical learning. 2nd ed. New York/Berlin/Heidelberg: Springer; 2008.

[23] Duda R, Hart P, Stork D. Pattern classification. Hoboken: John Wiley & Sons; 2001.

[24] Tibshirani R. Regression shrinkage and selection via the lasso. J R Stat Soc Ser B 1996;58:267–88. https://www.jstor.org/stable/2346178.

[25] Hoerl AE, Kennard RW. Ridge regression: biased estimation for nonorthogonal problems. Technometrics 1970;12(1):55–67. https://doi.org/10.2307/1267351.

[26] Zou H, Hastie T. Regularization and variable selection via the elastic net. J Royal Stat Soc Ser B 2005;67(2):301–20. https://doi.org/10.1111/j.1467-9868.2005.00503.x.

[27] Breiman L, Friedman JH, Olshen RA, Stone CJ. Classification and regression trees. 1st ed. Milton Park, UK: Routledge; 1984. https://doi.org/10.1201/9781315139470.

[28] Ho TK. The random subspace method for constructing decision forests. IEEE Trans Pattern Analysis Mach Intell 1998;20:832–44. https://doi.org/10.1109/34.709601.

[29] Noble WS. What is a support vector machine? Nat Biotechnol 2006;24(12):1565–7. https://doi.org/10.1038/nbt1206-1565.

[30] Lilleker JB, Vencovsky J, Wang G, et al. The EuroMyositis registry: an international collaborative tool to facilitate myositis research. Ann Rheum Dis 2018;77:30–9. https://doi.org/10.1136/annrheumdis-2017-21186.

[31] Guimarães F, Yildirim R, Isenberg DA. Long-term survival of patients with idiopathic inflammatory myopathies: anatomy of a single-Centre cohort. Clin Exp Rheumatol 2023;41(2):322–9. https://doi.org/10.55563/clinexprheumatol/486yh4.

[32] Won Huh J, Soon Kim D, Keun Lee C, et al. Two distinct clinical types of interstitial lung disease associated with polymyositis-dermatomyositis. Respir Med 2007;101 (8):1761–9. https://doi.org/10.1016/j.rmed.2007.02.017.

[33] Li Y, Gao X, Li Y, et al. Predictors and mortality of rapidly progressive interstitial lung disease in patients with idiopathic inflammatory myopathy: a series of 474 patients. Front Med (Lausanne) 2020;7:363. https://doi.org/10.3389/fmed.2020.00363.

[34] Danieli MG, Verga JU, Mezzanotte C, et al. Replacement and immunomodulatory activities of 20% subcutaneous immunoglobulin treatment: a single-center retrospective study in autoimmune myositis and CVID patients. Front Immunol 2022;12:805705. https://doi.org/10.3389/fimmu.2021.805705.

[35] van Dijkhuizen EP, Deakin CT, Wedderburn LR, De Iorio M. Modelling disease activity in juvenile dermatomyositis: a Bayesian approach. Stat Meth Med Res 2019;28(1):35–49. https://doi.org/10.1177/0962280217713233.

[36] Rider LG, Lachenbruch PA, Monroe JB, et al. IMACS group. Damage extent and predictors in adult and juvenile dermatomyositis and polymyositis as determined with the myositis damage index. Arthritis Rheum 2009;60(11):3425–35. https://doi.org/10.1002/art.24904.

[37] Mathiesen P, Hegaard H, Herlin T, Zak M, Pedersen FK, Nielsen S. Long-term outcome in patients with juvenile dermatomyositis: a cross-sectional follow-up study. Scand J Rheumatol 2012;41(1):50–8. https://doi.org/10.3109/03009742.2011.608376.

[38] Bruce B, Fries JF. The health assessment questionnaire (HAQ). Clin Exp Rheumatol 2005;23(5 Suppl 39):S14–8 [PMID: 16273780].

[39] Ponyi A, Borgulya G, Constantin T, Váncsa A, Gergely L, Dankó K. Functional outcome and quality of life in adult patients with idiopathic inflammatory myositis. Rheumatology (Oxford) 2005;44(1):83–8. https://doi.org/10.1093/rheumatology/keh404.

[40] Vincze A, Bodoki L, Szabó K, et al. The risk of fracture and prevalence of osteoporosis is elevated in patients with idiopathic inflammatory myopathies: cross-sectional study from a single Hungarian center. BMC Musculoskelet Disord 2020;21(1):426. https://doi.org/10.1186/s12891-020-03448-2.

[41] Cordeiro RA, Fischer FM, Shinjo SK. Work situation, work ability and expectation of returning to work in patients with systemic autoimmune myopathies. Rheumatology (Oxford) 2021;62(2):785–93. https://doi.org/10.1093/rheumatology/keac389.

[42] Rider LG, Koziol D, Giannini EH, et al. Validation of manual muscle testing and a subset of eight muscles for adult and juvenile idiopathic inflammatory myopathies.

Arthritis Care Res (Hoboken) 2010;62(4):465–72. https://doi.org/10.1002/acr.20035.
[43] Espinosa-Ortega F, Holmqvist M, Dastmalchi M, Lundberg IE, Alexanderson H. Factors associated with treatment response in patients with idiopathic inflammatory myopathies: a registry-based study. Arthritis Care Res (Hoboken) 2022;74(3):468–77. https://doi.org/10.1002/acr.24498.
[44] Landon-Cardinal O, Bachasson D, Guillaume-Jugnot P, et al. Relationship between change in physical activity and in clinical status in patients with idiopathic inflammatory myopathy: a prospective cohort study. Semin Arthritis Rheum 2020;50(5):1140–9. https://doi.org/10.1016/j.semarthrit.2020.06.014.
[45] Aggarwal R, Rider LG, Ruperto N, International Myositis Assessment and Clinical Studies Group and the Paediatric Rheumatology International Trials Organisation, et al. 2016 American College of Rheumatology/European League Against Rheumatism criteria for minimal, moderate, and major clinical response in adult dermatomyositis and polymyositis: An International Myositis Assessment and Clinical Studies Group/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. Ann Rheum Dis 2017;76(5):792–801. https://doi.org/10.1136/annrheumdis-2017-211400.
[46] Rider LG, Aggarwal R, Machado PM, et al. Update on outcome assessment in myositis. Nat Rev Rheumatol 2018;14(5):303–18. https://doi.org/10.1038/nrrheum.2018.33.
[47] Eng SWM, Olazagasti JM, Goldenberg A, et al. A clinically and biologically based subclassification of the idiopathic inflammatory myopathies using machine learning. ACR Open Rheumatol 2020;2(3):158–66. https://doi.org/10.1002/acr2.1111.