

The Refractory DermatoMyositis Index (ReDMI): a clinical tool to predict refractory disease in patients with dermatomyositis

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Abstract Objectives

To prospectively address the predictive features of refractory dermatomyositis (DM) and to construct and internally validate a clinical predictive index to timely identify patients at risk of this complication.

Methods

We recruited 168 patients with DM in a tertiary care centre in Mexico, and prospectively followed them, looking for the primary outcome, which was the diagnosis of refractory disease, defined as persistent disease activity three months after an adequate treatment course with glucocorticoids and at least one immunosuppressant. A logistic regression analysis was performed to calculate the odds ratios (OR) with 95% confidence interval (95% CI) of each predictive feature and to construct the Refractory DermatoMyositis Index (ReDMI).

Results

One hundred twenty-one (72%) patients were women, and the most frequent myositis-specific antibody was Mi2 (23.9%). Fifty-seven patients (33.9%) developed refractory disease. The positivity for anti-TIF1- γ (3.76 (1.17-13.3), $p=0.029$), the gastrointestinal disease activity (visual analogue scale) (1.11 (1.004-1.249), $p=0.04$), and alopecia (2.5 (1.11-5.7), $p=0.026$) were the refractoriness predictive factors. ReDMI predicted refractory disease with an OR of 3.57 (95% CI 1.71-7.59), an optimism corrected area under the curve of 0.67 with good internal validity and calibration.

Conclusion

After external validation, the ReDMI may be a useful clinical tool to timely detect DM patients at risk of developing refractory disease who may be candidates to receive an early more aggressive therapy.

Key words

idiopathic inflammatory myopathies, dermatomyositis, refractory disease, predictive index, anti-TIF1- γ

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Introduction

Idiopathic inflammatory myopathies (IIM) are a group of systemic autoimmune diseases characterised by muscle weakness and a myriad of extra muscular features (1). According to the positivity of myositis specific (MSA) and associated antibodies (MAA), the clinical, and histopathological features; the following phenotypes are recognized: Dermatomyositis (DM), anti-synthetase syndrome (ASSD), immune mediated necrotizing myopathy (IMNM), inclusion body myositis (IBM), overlap myositis (OM) and polymyositis (PM), currently a diagnosis of exclusion (2).

In patients with IIM, the treatment choice depends on the type and severity of the clinical features (3). Nonetheless, due to the rarity of IIM, there is a lack of clinical trials and guidelines for their treatment (3). Most recommendations include IV or oral glucocorticoids along with methotrexate (MTX) and/or azathioprine as first line therapies and the use of intravenous immunoglobulin (IVIg) for the treatment of resistant IIM (3). Second line treatments are calcineurin inhibitors, cyclophosphamide, whilst third line therapies include mycophenolate mofetil, and rituximab (3).

Notwithstanding the available therapeutic options for patients with IIM, their treatment with conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) remains suboptimal. Some clinical features of patients with IIM may be refractory to csDMARDs, making them candidates to biological treatment after a systematic approach (4). For instance, a recent study involving patients with anti-Jo1+ AS showed that the proportion of patients achieving low disease activity was 46.9% in those receiving anti-CD20mAbs *versus* 22.4% in those treated with csDMARDs, $p=0.011$ (5). Other csDMARDs like azathioprine are discontinued in up to 41% of patients due to inefficacy (6) and MTX fails to control cutaneous disease in up to 64.3% (7).

In IIM, persistent disease activity leads to damage accrual, which highly correlates with disability (8). Male sex, severe muscle weakness, concurrent interstitial lung disease (ILD) and fatty

infiltration on magnetic resonance image were described as risk factors for refractory IMNM in 48 patients (9); however, larger studies encompassing a considerable amount of patients with DM are lacking. Therefore, the aim of the present study was to prospectively evaluate the risk factors for refractory disease at DM diagnosis and to construct a clinical predictive index to promptly identify these patients.

Methods

For this prospective cohort study, we recruited 168 adult patients who were prospectively followed up at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INC-MNSZ), a tertiary care referral centre for patients with IIM in Mexico. All patients are part of the Myositis Translational Research Cohort Salvador Zubirán (MYOTReCSZ) and are classified as DM according to 2017 ACR/EULAR classification criteria (10). We excluded patients with any kind of juvenile myositis, ASSD, PM, IMNM, IBM, and patients without adherence to immunosuppressive therapy as documented by interview in each consult. The study was approved by the Ethics Committee of INC-MNSZ (Ref. 2984), and all participants provided written informed consent.

Baseline assessment was defined as the time of study enrolment, and the follow-up period extended until the diagnosis of refractory disease or the last available visit. At recruitment, two certified rheumatologists (J.T.-R., and D.G.-M.) evaluated the international myositis assessment and clinical studies group (IMACS) core set measures, which are the physician's and patient's visual analogue scale (VAS) of disease activity, the manual muscle test 8 (MMT8), the health assessment questionnaire disability index (HAQ-DI), the muscle enzymes (ALT, AST, CPK, LDH and aldolase), and the VAS of extra-muscular disease activity. Also, we addressed the myositis disease activity assessment tool (MDAAT), the myositis intention to treat index (MITAX), and the myositis damage index (MDI) (11). We registered the laboratory features (before or after starting im-

Competing interests: none declared.

munosuppressive therapies, depending on patients' admission to the hospital), type and dose of immunosuppressive therapy and the MSA and MAA using the EUROLINE Profile Autoimmune Inflammatory Myopathies from Euroimmune (Lübeck, Germany).

We prospectively evaluated the patients every four months or more frequently depending on disease activity, looking for the primary outcome, which was the diagnosis of refractory disease, defined as persistent disease activity three months after an adequate treatment course with glucocorticoids and at least one immunosuppressant [mostly methotrexate (MTX), azathioprine (AZA) and mycophenolate mofetil (MMF)] (12). At the end of follow-up, which was when the diagnosis of refractory disease was made or at the last clinical visit for patients without this primary outcome, the damage accrual and the cumulative prednisone dose were assessed.

Statistical analysis

We depicted quantitative variables as medians and interquartile range (IQR) and compared them using the Mann-Whitney U test. Categorical variables were expressed as proportions, and we assessed the associations between them using the Chi-square test. Independent predictors of refractory disease were identified using binary logistic regression to calculate odds ratios (ORs) with 95% confidence intervals (CIs) and selected the best model using the Akaike information criteria (AIC). The Refractory DermatoMyositis Index (ReDMI) was derived from independent variables that remained significant in the multivariate model. The probability of refractory disease was estimated directly from the adjusted logistic model. Model performance was evaluated using calibration statistics, the Nagelkerke R², and the area under the receiver operating characteristic (ROC) curve (AUC). The ReDMI was internally validated using bootstrap resampling. Statistical analysis was made using R: a language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria, URL <http://www.R-project.org/>.

Table I. Baseline clinical and laboratory features of IIM patients with refractory and non-refractory disease.

Variable	Refractory disease		<i>p</i>
	Absent n=111 Median (IQR)	Present n=57 Median (IQR)	
Women, n (%)	80 (72)	41 (72)	0.7
Age (years)	44 (31-56)	42 (32-53)	0.73
Time since disease diagnosis (months)	5 (2-9.75)	4 (1-9)	0.15
Laboratory features			
Leukocytes (x10 ⁹ /L)	6.6 (5.0-8.7)	5.7 (4.7-7.5)	0.11
Lymphocytes (x10 ⁹ /L)	1060 (660-1560)	910 (550-1380)	0.20
Neutrophils (x10 ⁹ /L)	4430 (3171-6510)	3968 (2843-5485)	0.28
Neutrophil to lymphocyte ratio (AU)	4 (2-9)	5 (2-8)	0.46
Monocytes (x10 ⁶ /L)	460 (340-643)	420 (315-545)	0.24
Haemoglobin (g/dL)	13.9 (12.3-15.1)	13.5 (12.2-14.9)	0.54
Platelets (x10 ⁹ /L)	235 (190-287)	238 (183-286)	0.54
Albumin (g/dL)	3.83 (3.24-4.17)	3.7 (3.12-4)	0.52
Globulins (g/dL)	3 (2.64-3.44)	3.01 (2.51-3.43)	0.46
Ferritin (ng/mL)	303 (69-1357)	219 (121-1318)	0.83
CPK (U/L)	178 (73-1439)	268 (95-1614)	0.38
AST (U/L)	51 (27-146)	66 (25-148)	0.83
ALT (U/L)	41 (22-102)	49 (28-87)	0.44
Aldolase (U/L)	8 (5-15)	16 (7-29)	0.01
LDH (140-271 U/L)	279 (198-588)	380 (237-815)	0.12
Creatinine (mg/dL)	0.57 (0.40-0.74)	0.51 (0.40-0.69)	0.63
Immunosuppressive therapy			
Prednisone dose (mg/d)	10 (0-50)	21 (5-50)	0.08
Azathioprine dose (mg/d)	0 (0-0)	0 (0-50)	0.27
Methotrexate dose (mg/week)	0 (0-15)	0 (0-20)	0.10
Antimalarials dose (mg/d)	0 (0-200)	0 (0-200)	0.10
Mycophenolate mofetil dose (gr/d)	0 (0-0)	0 (0-0)	0.46
Tacrolimus dose (mg/d)	0 (0-0)	0 (0-0)	0.08

IQR: interquartile range; AU: arbitrary units.

Results

One hundred twenty-one (72%) patients were women. The median (IQR) of age at recruitment was 44 (32-54) years and the most frequent myositis-specific autoantibody was Mi2 (23.9%). After a median follow up time of 46 months, 57 patients (33.9%) developed refractory disease, 38 (66.6%) in the muscle domain and 19 (33.3%) in the cutaneous domain. There was not a statistically significant difference in the follow-up time of patients with and without the primary outcome. In Table I, we depict the baseline clinical and laboratory features of DM patients who developed refractory disease and those who did not. At baseline, patients with refractory disease had higher aldolase (16 U (7-29) vs. 8 (5-15), *p*=0.01). In Table II, we show the baseline disease activity and damage accrual parameters in patients with DM who prospectively developed refractory disease in comparison to those who did not. Regarding disease activity, patients who prospectively developed refrac-

tory disease had a higher baseline MIMAX (0.30 (0.14-0.49) vs. 0.24 (0.0-0.38), *p*=0.04), as reflected in a higher gastrointestinal disease activity (table 2). Also, they had more frequently positive anti-TIF1- γ antibodies (11 (17.1%) vs. 5 (3.6%), *p*=0.003), dysphagia (29 (51%) vs. 39 (35%) *p*=0.049), and less frequently calcinosis (2 (3.1%) vs. 16 (11.7%), *p*=0.018). Patients with refractory DM were more frequently under prednisone treatment (49 (86%) vs. 72 (65%) *p*=0.002) or had already received a dose of rituximab (2 (3.5%) vs. 0 (0%) *p*=0.036) or IVIg (7 (12%) vs. 4 (3.6%) *p*=0.037).

At the end of follow-up, DM patients who developed refractory disease had higher cumulative prednisone dose (15 gr (9-26) vs. 10 (6-17) *p*=0.001) and had been treated with a higher number of lines of treatment (2 (1-3) vs. 0 (0-0) *p*<0.0001) (Table III).

The ReDMI was constructed from three independent predictors: anti-TIF1- γ positivity (3.76 (1.17-13.3), *p*=0.029), visual analogue scale of gastrointesti-

Table II. Baseline disease activity and damage accrual of IIM according to prospective development of refractory disease.

Variable	Refractory disease		<i>p</i>
	Absent n=111 Median (IQR)	Present n=57 Median (IQR)	
MMT8	136 (110-150)	128 (109-146)	0.23
HAQ-DI	2 (0.88-3)	2.25 (0.8-3)	0.47
Active CDASI	10 (3-21)	10 (3-20)	0.90
Chronic CDASI	2 (0-5)	2 (0-5)	0.82
MDAAT			
Constitutional (VAS)	3 (0-7)	3 (0-5)	0.94
Constitutional (Sum)	4 (0-8)	4 (0-8)	0.29
Cutaneous (VAS)	5 (2-7)	5 (2-7)	0.89
Cutaneous (Sum)	12 (4-16)	12 (7-20)	0.07
Skeletal (VAS)	0 (0-0)	0 (0-3)	0.10
Skeletal (Sum)	0 (0-2)	0 (0-8)	0.16
Gastrointestinal (VAS)	0 (0-3)	2 (0-5)	0.001
Gastrointestinal (Sum)	0 (0-4)	4 (0-8)	0.006
Pulmonary (VAS)	0 (0-2.5)	0 (0-4)	0.23
Pulmonary (Sum)	0 (0-4)	0 (0-8)	0.12
Cardiovascular (VAS)	0 (0-0)	0 (0-0)	0.37
Cardiovascular (Sum)	0 (0-0)	0 (0-0)	0.35
Other (VAS)	0 (0-3)	0 (0-5)	0.37
Other (Sum)	0 (0-4)	0 (0-4)	0.32
Extra-muscular disease activity (VAS)	3 (1-5)	3 (2-4)	0.49
Muscular (VAS)	5 (2-7)	5 (2-8)	0.43
Muscular (Sum)	8 (4-12)	12 (4-16)	0.23
MYOACT	0.17 (0.07-0.28)	0.21 (0.1-0.35)	0.11
MITAX	0.24 (0.11-0.38)	0.30 (0.14-0.49)	0.04
MDI			
Muscular (VAS)	1 (0-3)	1 (0-3)	0.47
Muscular (Sum)	1 (0-2)	1 (0-2)	0.21
Skeletal (VAS)	0 (0-0)	0 (0-0)	0.46
Skeletal (Sum)	0 (0-0)	0 (0-0)	0.55
Cutaneous (VAS)	1 (0-3)	1 (0-3)	0.63
Cutaneous (Sum)	1 (0-1.5)	1 (0-1)	0.36
Gastrointestinal (VAS)	0 (0-0)	0 (0-0)	0.37
Gastrointestinal (Sum)	0 (0-0)	0 (0-0)	0.60
Pulmonary (VAS)	0 (0-0)	0 (0-0)	0.59
Pulmonary (Sum)	0 (0-0)	0 (0-0)	0.49
Cardiovascular (VAS)	0 (0-0)	0 (0-0)	0.37
Cardiovascular (Sum)	0 (0-0)	0 (0-0)	0.36
Peripheral vascular (VAS)	0 (0-0)	0 (0-0)	0.48
Peripheral vascular (Sum)	0 (0-0)	0 (0-0)	0.48
Endocrine (VAS)	0 (0-0)	0 (0-0)	0.26
Endocrine (Sum)	0 (0-0)	0 (0-0)	0.78
Ocular (VAS)	0 (0-0)	0 (0-0)	0.21
Ocular (Sum)	0 (0-0)	0 (0-0)	0.21
Infectious (VAS)	0 (0-0)	0 (0-0)	0.44
Infectious (Sum)	0 (0-0)	0 (0-0)	0.94
Malignancy (VAS)	0 (0-0)	0 (0-0)	0.97
Malignancy (Sum)	0 (0-0)	0 (0-0)	0.77
Other (VAS)	0 (0-0)	0 (0-0)	0.40
Other (Sum)	0 (0-0)	0 (0-0)	0.66
Global damage (VAS)	2 (0-3)	2 (1-3)	0.35
Damage extension	0.05 (0.0-0.13)	0.06 (0.01-0.11)	0.94
Damage severity	0.04 (0.0-0.07)	0.04 (0.02-0.07)	0.61
Extended damage	0.07 (0.0-0.14)	0.08 (0.0-0.14)	0.39

VAS: visual analogue scale; MMT8: manual muscle testing 8; HAQ-DI: Health Assessment Questionnaire-Disability Index; CDASI: Cutaneous Dermatomyositis Disease Area and Severity Index; MDAAT: myositis disease activity assessment tool; MYOACT: myositis disease activity assessment visual analogue scales; MITAX: myositis intention to treat; MDI: myositis damage index.

nal disease activity (1.11 (1.004-1.249), *p*=0.04), and alopecia (2.5 (1.11-5.7), *p*=0.026) (Fig. 1), which were identified in the multivariate logistic regres-

sion model (Table IV). The index was retained as a continuous variable, allowing the probability of refractory disease to be estimated directly from

the adjusted model without predefined cutoffs. The ReDMI was significantly associated with treatment refractoriness ($\chi^2=13.94$, *p*<0.001) with an odds ratio of 3.57 (95% CI 1.71-7.59). Model performance metrics showed a Nagelkerke R² of 0.13 and an AUC of 0.67, consistent with moderate discriminative capacity, with a Somers' Dxy of 0.34. Bootstrap validation confirmed internal robustness (Fig. 2). Calibration analysis demonstrated good concordance between predicted and observed probabilities, with low prediction error (mean absolute error (MAE)=0.036) and mean squared error (MSE=0.002)). Finally, the predicted probability of refractory disease increased progressively with the ReDMI score, ranging from approximately 0.25 for the lowest index values to 0.87 for the highest. This gradient demonstrates that higher index scores correspond to a markedly increased likelihood of treatment refractoriness (Fig. 3).

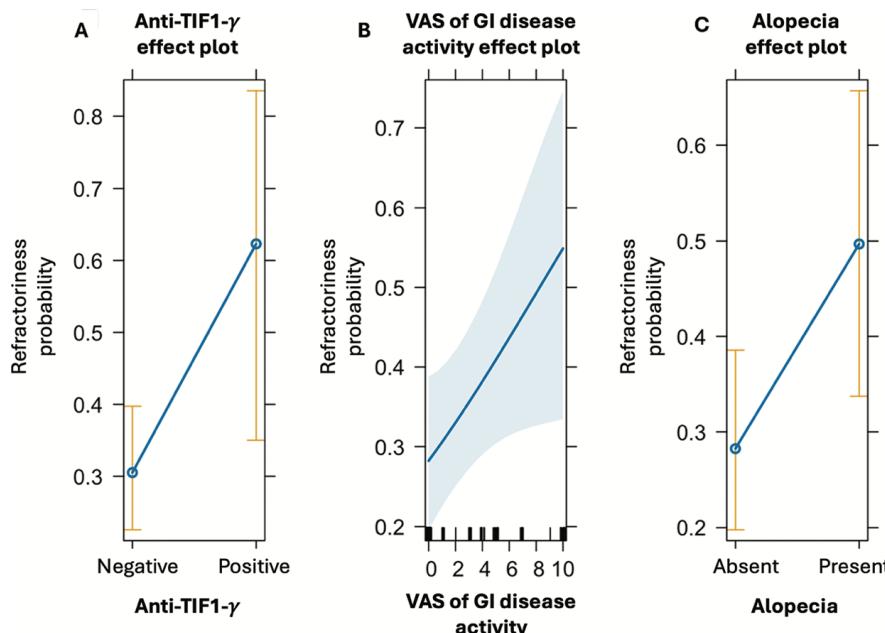
Discussion

To the best of our knowledge, this is the first study to prospectively address the risk factors for refractory disease in a cohort of patients with DM. Many studies have assessed the prognostic factors of patients with IIM. The diagnosis of polymyositis, older age, severe weakness, longer duration of weakness prior to diagnosis and associated malignancy or cardiac disease are described as risk factors for poor response to therapy in these patients (13). In this study, we identified a clinical phenotype closely related to refractory disease, which is TIF1- γ + DM with alopecia and severe gastrointestinal disease activity (dysphagia). Interestingly, we found that patients without refractory disease had more frequently calcinosis, which suggests a more insidious disease course, since this clinical manifestation occurs after a mean time since disease diagnosis of 43.7 months (1-288) (14).

The ReDMI encompasses clinical features that may be more severe or more frequent in patients with anti-TIF1- γ + DM. Small studies addressing the scalp involvement in DM have shown alopecia in 43-48.9% of patients, being the anti-TIF1- γ a MSA closely related to

Table III. Variables evaluated at the end of follow-up.

Variable	Refractory disease		<i>p</i>
	Absent n=111	Present n=57	
Cumulative prednisone dose (gr)	10 (6-17)	15 (9-26)	0.001
Treatment lines (#)	0 (0-0)	2 (1-3)	<0.0001
Total follow-up (months)	46 (7-87)	46 (9-76)	0.87
Final damage extension	0.06 (0.03-0.14)	0.08 (0.03-0.13)	0.15
Final damage severity	0.05 (0.01-0.09)	0.05 (0.03-0.09)	0.19
Final extended damage	0.08 (0.0-0.16)	0.08 (0.07-0.15)	0.12

**Fig. 1.** Graphical depiction of predictive clinical variables associated with refractory disease in dermatomyositis. The figures illustrate clinical factors linked to the development of refractory disease. **A.** Anti-TIF1- γ positivity. **B.** Visual analogue scale (VAS) of gastrointestinal (GI) disease activity. **C.** Alopecia.**Table IV.** Univariate and multivariate analysis to predict refractory disease probability in patients with DM.

Variable	Univariate OR (95% CI)	<i>p</i>	Multivariate OR (95% CI)	<i>p</i>
Positive anti-TIF1- γ	5.05 (1.71-16.99)	0.003	3.76 (1.17-13.3)	0.029
Alopecia	2 (0.99-4.04)	0.049	2.50 (1.11-5.7)	0.026
VAS of gastrointestinal disease activity	1.13 (1.03-1.24)	0.008	1.11 (1.00-1.24)	0.041
Calcinosis	0.21 (0.03-0.79)	0.018		
Dysphagia	1.91 (1.00-3.67)	0.049		
Aldolase	1.03 (1.00-1.07)	0.043		
Sum of cutaneous disease activity	1.04 (1.00-1.08)	0.033		
Sum of gastrointestinal disease activity	1.12 (1.03-1.23)	0.006		
MITAX	5.21 (1.01-27.77)	0.047		
Prednisone use	3.31 (1.49-8.19)	0.002		
IVIg use	3.74 (1.08-14.84)	0.037		

VAS: visual analogue scale.

this symptom (83.3%) (15-17), which explains alopecia as a risk factor of refractoriness.

Dysphagia is reported in 10-73% of patients with IIM (18) and, along with treatment delay, fever, acute pulmonary

infiltrates and cardiac involvement, is one of the main risk factors for mortality in these patients (19). Previous studies have shown that the positivity for anti-PM/Scl 75/100 (20), muscle weakness, aspiration pneumonia and

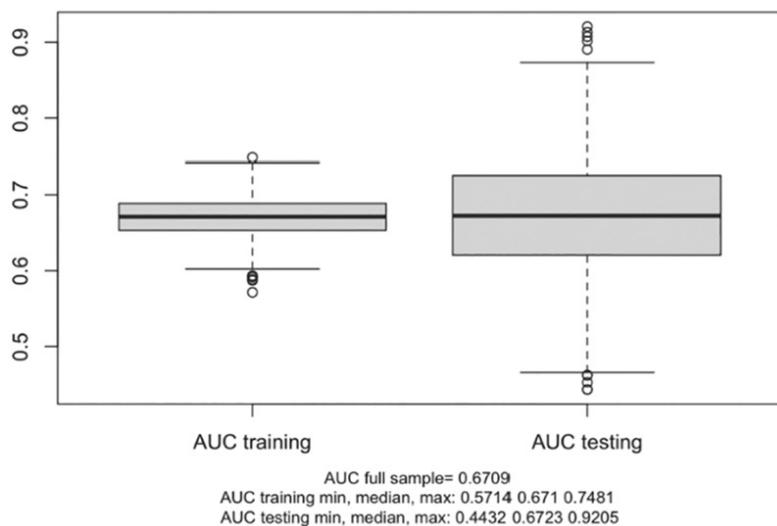
ventilatory insufficiency (21) are risk factors for refractory dysphagia in IIM, highlighting its importance as a treatment resistant clinical feature.

With the discovery of the MSA and MAA, and the recognition of defined clinical phenotypes, new prognostic factors of IIM have been described. For instance, patients with anti-synthetase and anti-SRP antibodies are more likely to have a partial response to prednisone, whilst patients with anti-Mi2 antibodies respond more favourably to treatment (19). The positivity for anti-TIF1- γ antibodies has been associated to mortality in IIM (22). According to our results, previous studies have found an association between anti-TIF1- γ and severe dysphagia (23, 24), showing involvement of the lower oesophageal sphincter in patients with this autoantibody (25). Furthermore, in a previous study of patients with juvenile dermatomyositis (jDM), it was found that the positivity for anti-TIF1- γ , dysphagia, pulmonary, cardiac and gastrointestinal features, weight loss and higher levels of aldolase were associated to a longer time for remission achievement (26), which is similar to our results.

The construction of a refractory disease predictive index in DM is of great relevance in the management of these patients, because it may help to identify patients who require an early more aggressive treatment. For instance, the efficacy of RTX in patients with refractory disease (inadequate response to an adequate course of glucocorticoids and intolerance or inefficacy of at least one immunosuppressant) (27, 28) has been proven. In a recent meta-analysis, the pooled estimated effectiveness of RTX in refractory myositis was 80% (95% CI 75-85%), although there was a potential publication bias (29). Furthermore, recent data has shown that the early start of IVIg or RTX in patients with IIM improves prognosis with an enhanced muscle strength (30, 31). In a study with real life data, it was demonstrated that the factors associated to a higher response probability in IIM patients who were treated with IVIg for refractory disease were older age, lesser time since disease diagnosis, myalgia, higher levels of CPK and

A

Cross-validated AUC
n of iterations: 1000



B

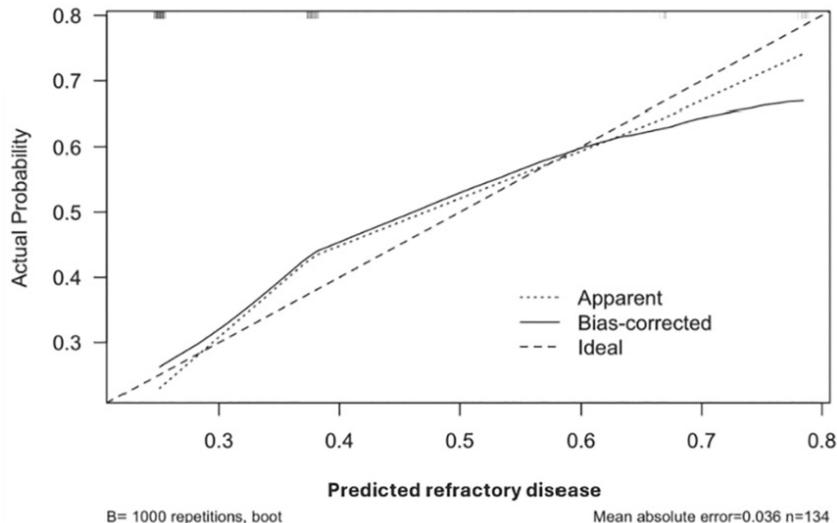


Fig. 2. ReDMI internal validation and calibration. **A.** Boxplots showing AUC values in the training (left) and test sets (right) over 1,000 bootstrap iterations. The model showed a median AUC of 0.671 in the training sets and 0.6723 in the testing sets, with overall consistency across iterations. **B.** Calibration graph of the predictive model for refractory disease. The dashed line represents the ideal calibration, the dotted line represents the apparent calibration (uncorrected model), and the solid line represents the bootstrap-adjusted calibration (1,000 replicates). The calibration slope was 1.07, close to the ideal value of 1, and the calibration intercept was 0.00, indicating no systematic bias. The Emax statistic was 0.023, while the mean absolute error (MAE) and mean squared error (MSE) were 0.036 and 0.002, respectively, reflecting low prediction error. The progressive increase in probability confirms the adequate calibration and capacity of the index to discriminate.

LDH, whilst patients with refractory cutaneous disease had less probability to respond (32). Therefore, the ReDMI may be an important tool for the timely identification of patients at risk of having refractory disease who may benefit from the early application of these interventions to improve their treatment response rate.

This is the first prospective cohort study with a considerable number of

well characterised DM patients assessing the risk factors for refractory disease. Nonetheless, this study has certain limitations. Given its unicentric design and the exclusive inclusion of Hispanic patients, the generalizability of our findings is limited. Besides, the ReDMI should be externally validated before it can become widely used in clinical practice.

In conclusion, the positivity for anti-

TIF1- γ , increased levels of gastrointestinal disease activity and the presence of alopecia are independent risk factors for refractory disease in DM. After internal validation, the composite index ReDMI shows adequate predictive capacity and reliable calibration, supporting its use as a clinical support tool for the early identification of patients at risk of therapeutic refractoriness who may be candidates to receive an early more aggressive therapy.

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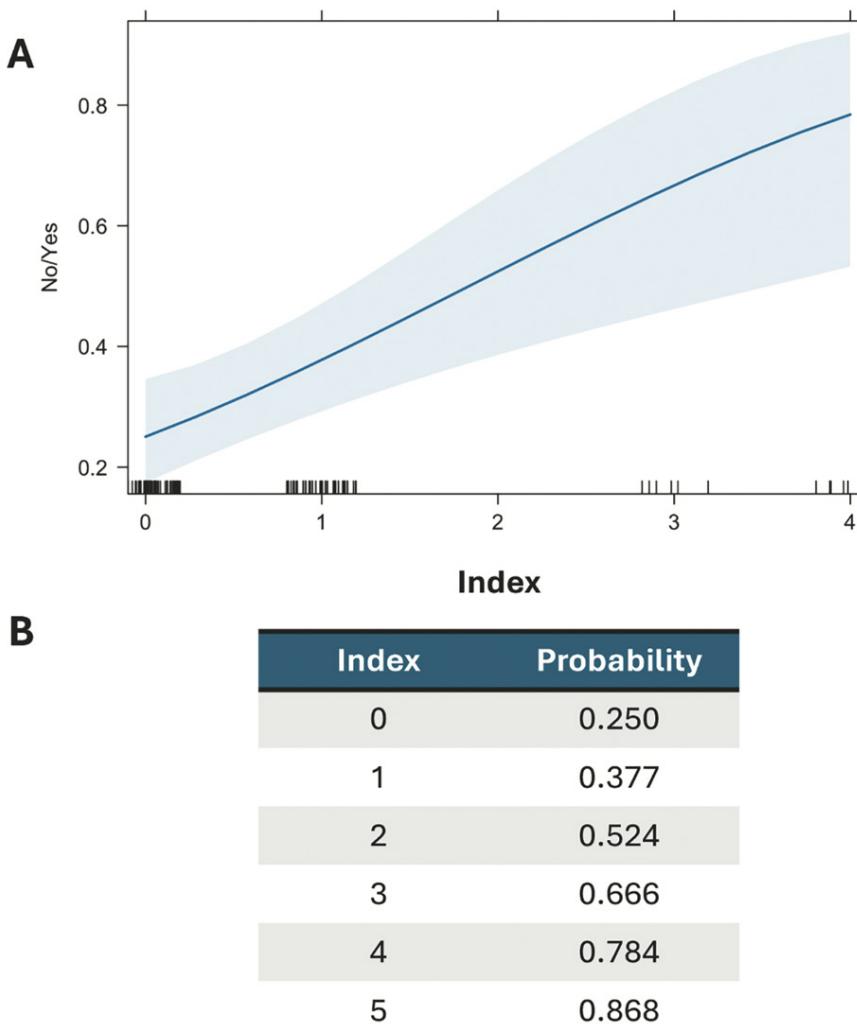


Fig. 3. Relationship between the composed index and the predicted probability of refractory disease. **A.** The blue line represents the fitted logistic regression curve, the shaded area shows the 95% confidence interval and the rug marks represent the distribution of observed index values for each patient. **B.** A progressive increase in the predicted probability of refractory disease is observed as the index increases, confirming the predictive ability of the model ($p<0.001$).

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