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ORIGINAL ARTICLE

Long-term pulmonary outcomes and mortality in idiopathic inflammatory myopathies associated with interstitial lung disease

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Abstract

Objective To study prognostic factors in different types of idiopathic inflammatory myopathies (IIM) associated with interstitial lung disease (ILD).

Patients and methods Multicenter retrospective study of a Spanish cohort of patients diagnosed with IIM. Patients were classified into four categories: polymyositis (PM), dermatomyositis (DM), antisynthetase syndrome (ASS), and overlap myositis (OM). Sociodemographic data, clinical characteristics, antibodies, and treatments were collected. Cox regression models were calculated to identify factors associated with mortality, the necessity for long-term oxygen therapy (LTOT), and deterioration in respiratory function tests (RFT).

Results The number of patients included was 478, of whom 112 (23.4%) suffered from ILD: 17% PM, 16% DM, 45% ASS, and 22% OM. Factors associated with mortality in the multivariate analysis were clinically meaningful progression of ILD after 3 months (CMP 3m) (hazard ratio (HR) 9.48, $p = 0.005$), severe infections (HR 6.41, $p = 0.016$), heliotrope erythema (HR 31.1, $p = 0.002$), delay in diagnosis (HR 1.29; $p = 0.011$), and Raynaud's phenomenon (HR 11.9, $p = 0.007$). However, being female (HR 0.19, $p = 0.044$) and positivity solely for ANAs (HR 0.08, $p = 0.008$) presented a protective effect. CMP 3m (HR 22.7, $p = 0.027$) was associated with the need for LTOT, while basal aldolase (HR 0.90; $p = 0.049$) had a protective effect. Likewise, joint manifestations (HR 0.04, $p = 0.034$) were shown to reduce risk of deterioration in RFT.

Conclusions CMP 3m, severe infections, delay in diagnosis, heliotrope erythema, and Raynaud's phenomenon were identified as factors of poor prognosis in different IIM associated with ILD.

Keywords Interstitial lung disease · Myositis · Oxygen therapy · Prognosis · Respiratory function tests · Survival

Introduction

Interstitial lung disease (ILD) is an extramuscular manifestation of idiopathic inflammatory myopathies (IIM) with a prevalence ranging between 20 and 78% depending on the methodology used for diagnosis [1]. ILD associated with IIM (IIM-ILD) causes functional limitations and increases the risk of comorbidities due to the severity of the illness and the need for additional corticosteroids and immunosuppressive drugs. The overall consequence is a significant deterioration in quality of life. Moreover, it is itself a risk factor for mortality [2–4]. These data highlight the need to identify patients with ILD who may suffer a worsening progression in order to establish the most suitable treatment early on and to avoid any associated damage. Results from several studies have showed that anti-MDA5 antibodies [5, 6], rapidly progressive lung disease (RPLD) [7], extensive inflammatory activity (as determined by high-resolution computed tomography (HRCT)) [8], highly elevated basal ferritin levels [9, 10], and low basal levels in respiratory function tests [11] are factors that increase the risk of a poor prognosis. However, the majority of these studies involved an Asian population, were single center in nature, or examined a specific type of myositis. Furthermore, follow-up was not always done long term, and only a poor prognostic outcome was analyzed in the majority of these studies. Therefore, the analysis of data obtained from a multicentric cohort, in a study developed at an European level, with different types of myopathies, and long-term follow-up

would lead to a better understanding of the illness' progression. We also believe that poor prognosis in clinical practice can be studied in different ways and may be associated with different factors.

The purpose of this study is to determine potential prognostic factors in different types of IIM associated with ILD through analysis of mortality, the need for long-term oxygen therapy (LTOT), and deteriorations in respiratory function tests (RFT).

Patients and methods

Design, scope, and participants

This is a retrospective longitudinal study of patients with IIM treated at rheumatology departments in Madrid. A hospital registry was created in February 2013 with information collected from medical histories (REMICAM registry). Patients' inclusion period in the REMICAM registry was March 2013–December 2014. Patients included were consecutive, non-selected, diagnosed with IIM during follow-up sometime between January 1980 and December 2014, without taking into account age at the start of the process. These patients met Bohan and Peter and/or Tanimoto criteria [12–14]. Patients with myopathies due to toxic cause, infectious causes, or neuromuscular disease were excluded. Length of follow-up was defined as the period of time between the date of diagnosis and the last visit to the rheumatology departments, the end of the observation period (December 2014), or the date of outcome in the study (death, LTOT required, and worsening of RFT). In the event of loss of contact during follow-up, an attempt was made to reach the patient by phone to learn his/her condition. When patients' information could not be retrieved, those cases were censored on the date of the last visit. If any patients changed hospitals, this was recorded to avoid loss of information. Patients were divided into two groups based on whether they presented any association with ILD or not. Patients with ILD were classified into four groups: primary polymyositis (PM), primary dermatomyositis (DM), overlap myositis (OM) syndrome, and antisynthetase (ASS) syndrome, defined by meet Bohan and Peter and/or Tanimoto criteria with anti-aminoacyl-transfer RNA synthetase (ARS) antibodies. Patients with OM had to meet IIM criteria in addition to criteria for one of the following systemic autoimmune diseases: rheumatoid arthritis [15], systemic sclerosis [16], systemic lupus erythematosus [17], mixed connective tissue disease [18], or Sjogren's syndrome [19]. Patients with cancer-associated myositis were included in the REMICAM registry but they were excluded for this specific study about ILD. This study was approved by the ethics committees of the participant hospitals and patients gave written informed consent.

Variables

Data on sociodemographic characteristics, comorbidities, smoking habit, clinical manifestations, laboratory parameters, treatment, and vital condition was collected. The methods of the study and the operational definitions of these variables have been previously published [20].

The following anti-ARS antibodies were identified by immunoblot or ELISA: anti-jo1, anti-PL7, and anti-PL12. Myositis-associated antibodies (anti-RNP and anti-Ro) were obtained by ELISA or chemiluminescence immunoassay. ANAs were defined as positive based on a titer ≥ 1:80 (by immunofluorescence) in at least two different samples. Antibody detection was conducted in the laboratory of each hospital.

Severe infections were defined as infections that required hospitalization or that resulted in death.

Diagnosis of ILD was made based on the presence of characteristic findings in chest X-ray and/or HRCT, and/or compatible RFT (≥ 10% decrease of the forced vital capacity or ≥ 15% decrease of diffusion respect to reference values), after excluding other causes.

ILD was categorized into the following subtypes depending on the result of HRCT pattern: usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP), organizing pneumonia (OP), acute interstitial pneumonia (AIP), and non-defined forms. According to a modification of OMERACT [21], the clinically meaningful progression after 3 months (CMP 3m) was defined as a decrease of the forced vital capacity (FVC) ≥ 10% or a decrease of FVC ≥ 5% and < 10% but with a decrease of diffusion (DLco) ≥ 15% as long as FVC and/or DLco after 3 months were < 80%.

Poor prognostic outcomes

Mortality

Cause of death was obtained from the medical history. In the event of loss of follow-up, the family was contacted by phone in order to know the patient's vital state, as well as the cause and date of death. Causes of death were classified as infection, cardiovascular event (arrhythmia, ischemic cardiopathy, acute ischemic or hemorrhagic stroke, pulmonary hypertension, cardiac failure, and pulmonary thromboembolism), ILD, and miscellany.

Necessity for long-term oxygen therapy

Necessity for LTOT was defined as oxygen administration for > 15 h/day in higher concentrations than in ambient air to improve tissue oxygenation of patients with chronic respiratory insufficiency.

Deterioration in respiratory function tests

A decrease of FVC ≥ 10%, or between 5 and 10% with a decrease of DLco ≥ 15%, compared with values obtained during the year following diagnosis [21].

Statistical analysis

Patients as a whole were described by using central tendency and dispersion measurements, as well as frequency and percentage distribution tables for quantitative and qualitative variables, respectively. Differences between patients with or without ILD, patients with ILD according to type of myositis, and according to type of ILD were analyzed. We used parametric or non-parametric tests depending upon the distribution of quantitative variables and differences of proportion obtained from chi-2 for the qualitative ones. Since they were multiple comparisons, the Bonferroni correction was applied ($p < 0.001$).

For the study of poor prognostic outcomes (mortality, necessity for LTOT, and deterioration of RFT), a survival analysis using the Kaplan–Meier method with a Mantel–Haenszel statistic (log-rank test) was conducted. Regarding mortality, the exposure period was established between the date of diagnosis and the date of death or last visit. The overall mortality rate was calculated as the ratio between the number of observed deaths and the cumulative survival time in patient-years. For LTOT, the exposure period was the period of time between the diagnosis date and the start date of oxygen therapy or date of last visit. Finally, the deterioration of RFT (FVC and DLco) was studied from date of first determination or the date of diagnosis to the date of last determination or the date of study closure. Cox proportional-hazards regression models were calculated to identify factors associated with the three outcome measurements. A hazard ratio (HR) was used together with a 95% confidence interval (CI) as a measurement of effect size. For multivariate models, the variable inclusion was made in accordance with those variables showing a $p < 0.20$ value in the bivariate analysis. The small sample size limited the inclusion of variables in the multivariate models; therefore, the most parsimonious model (lowest number of variables) containing less criteria of information (AIC and BIC) was chosen. The predictive capability of the adjusted model was calculated using the Harrell *C* statistic model.

Results

Participants

The number of patients included in the REMICAM registry was 478, mostly Caucasian (93%). Most of the patients met Bohan and Peter (99.6%), Tanimoto (97%), or both criteria (97%). The two cases that did not meet the Bohan and Peter criteria but of Tanimoto correspond to patients with ASS syndrome, with elevated muscle enzymes, arthritis, constitutional symptoms and ILD in both cases, and mechanic's hands in one case. Patients with IIM-ILD were 129 (27%), but we excluded from the study 16 patients who also had cancer and one patient who could not be classified within any IIM type. Finally, 112 (23.4%) patients with IIM-ILD made up the final sample for the analysis.

Epidemiological and clinical characteristics

Patients with ILD

The main epidemiological, clinical, and immune characteristics of patients with IIM-ILD compared with those without ILD are shown in Table 1. Only one patient was diagnosed of juvenile myositis and ILD. Patients with ILD had a significant higher age at diagnosis, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP), with a worse initial RFT ($p < 0.001$). In relation to clinical data, patients with ILD were characterized by significant increased frequency of arthritis, systemic manifestations, Raynaud's phenomenon (RP), ischemic ulcers, edema of hands, sclerodactyly, and mechanic's hands ($p < 0.001$). Regarding comorbidities and antibodies, pulmonary hypertension and anti-ARS antibodies were significant more frequent in patients with ILD ($p < 0.001$). Finally, patients with ILD used more synthetic immunosuppressive agents ($p < 0.001$) and three of them needed lung transplant.

Patients with ILD according to type of myopathy

Patients with ILD ($n = 112$) were classified as PM ($n = 19$; 17%), DM ($n = 18$; 16%), ASS ($n = 50$; 45%), and OM ($n = 25$; 22%). Out of the 50 patients with ASS, 44 presented anti-Jo-1 antibodies, three presented anti-PL7 antibodies, and another three presented anti-PL12 antibodies. The distribution of 25 patients with OM was 3 systemic lupus erythematosus, 10 systemic sclerosis, 9 mixed connective tissue disease, and 3 Sjogren's syndrome. Regarding differences in clinical characteristics between groups, a lower frequency of arthritis in PM ($p < 0.0001$), a higher frequency of sclerodactyly in OM and ASS ($p < 0.0001$), and a higher frequency of mechanic's hands in DM and ASS ($p < 0.0001$) were found. Regarding antibodies, a higher frequency of ANA and anti-Ro in ASS (80 and 52%, respectively) and a higher frequency of anti-RNP in OM (46%) were found. No differences in RFT or between treatments were found (Table 2).

Patients with ILD in accordance with HRCT pattern

Out of 112 patients, 104 could be classified by HRCT. The distribution was as follows: UIP ($n = 45$; 43.3%), NSIP ($n =$

Table 1 Description of the total sample and according to the presence of interstitial lung disease

	Total ($N = 478$)	Non-ILD ($N = 349$)	ILD ($N = 129$)
Female sex	355 (74.3%)	257 (73.6%)	98 (76.0%)
Age at diagnosis (years)*	47.7 (26.7–62.1)	41.6 (17.1–60.4)	56.3 (42.7–65.8)
Caucasian race	446 (93.31%)	324 (92.84%)	122 (94.57%)
Years from symptom to diagnosis	0.29 (0.11–0.99)	0.25 (0.10–0.84)	0.32 (0.14–1.75)
Baseline CK (U/L)	761 (237–2640)	763 (227–2508)	737 (266–2773)
Baseline aldolase (U/L)	12 (7–21)	10.4 (7.0–19.0)	15.5 (9.1–28.5)
Maximum CRP in the first year (mg/dl)*	1.2 (0.1–5.4)	1.0 (0.1–4.0)	3.7 (1–9.3)
Maximum ESR in the first year (mm/h)*	34 (16–59)	29 (14–53)	47 (29–70)
DLco first year*	75 (53–80)	80 (75–80)	66 (53–80)
FVC first year*	80 (70–80)	80 (70–80)	70 (60–80)
Muscle weakness	456 (95.4%)	335 (96.0%)	121 (93.8%)
Systemic manifestations*	181 (39.3%)	111 (33.0%)	79 (56.0%)
Arthritis/arthralgia*	200 (42.5%)	120 (34.9%)	80 (63.0%)
Typical DM skin lesions			
Gottron papules	155 (32.4%)	122 (35.0%)	33 (25.6%)
Heliotrope rash	148 (31.0%)	120 (34.4%)	28 (21.7%)
Gottron sign	163 (34.2%)	133 (38.2%)	30 (23.4%)
Cutaneous vasculitis	34 (7.1%)	24 (6.9%)	10 (7.7%)
Cutaneous ulcers	16 (3.5%)	10 (3.0%)	6 (4.8%)
Ischemic ulcers*	36 (7.5%)	17 (4.9%)	19 (14.7%)
Periungual erythema	70 (15.1%)	44 (13.1%)	26 (20.5%)
Mechanic's hands*	72 (15.5%)	30 (8.9%)	42 (33.1%)
Calcinosis	50 (10.5%)	39 (11.3%)	11 (8.5%)
Edema of hands*	107 (23.1%)	62 (18.4%)	45 (35.4%)
Raynaud's phenomenon*	137 (28.8%)	77 (22.2%)	60 (46.5%)
Sclerodactyly*	62 (13.4%)	29 (8.9%)	33 (26.0%)
Hematological manifestations	135 (28.4%)	103 (29.7%)	32 (28.4%)
Dysphagia or reflux	144 (33.1%)	98 (28.1%)	46 (35.7%)
Cardiac manifestations	98 (20.5%)	58 (16.6%)	40 (31.0%)
Pulmonary hypertension*	38 (8.0%)	14 (4.0%)	24 (18.6%)
Renal manifestations	22 (4.6%)	15 (4.3%)	7 (5.4%)
Severe infections	113 (24.7%)	75 (22.5%)	38 (30.6%)
Cancer	69 (14.4%)	53 (15.2%)	16 (12.4%)
Current smoking	63 (19.4%)	43 (17.7%)	20 (24.4%)
Arterial hypertension	146 (31.1%)	100 (29.2%)	46 (36.2%)
Diabetes mellitus	58 (12.4%)	45 (13.2%)	13 (10.2%)
Pleurisy	13 (2.8%)	7 (2.0%)	6 (4.7%)
COPD	27 (5.8%)	17 (5.0%)	10 (7.9%)
Dyslipidemia	149 (31.8%)	102 (29.8%)	47 (37.0%)
Cardiovascular events	104 (22.3%)	63 (18.5%)	41 (32.3%)
Antibodies			
ANA	293 (62.1%)	193 (57.7%)	95 (73.6%)
Anti-ARS*	88 (19.3%)	31 (9.45%)	57 (44.5%)
Anti-Ro	11 (12.1%)	1 (10.0%)	10 (12.3%)
Anti-RNP	53 (12.4%)	36 (11.6%)	17 (14.5%)
Treatments			
Steroids	472 (98.7%)	343 (98.2%)	129 (100%)
Hydroxychloroquine	78 (16.3%)	62 (17.7%)	16 (12.4%)
Synthetic immunosuppressive agents*	355 (74.7%)	243(70.2%)	112 (86.8%)
Biologic immunosuppressive agents	55 (11.9%)	37 (11.2%)	18 (13.9%)
Immunoglobulin	79 (16.6%)	61 (17.6%)	18 (13.9%)

Muscle weakness was measured using the Medical Research Council scale. Data are presented as median and interquartile range (IQR) or *n* (%). Bonferroni correction was applied

CK creatine kinase, *ILD* interstitial lung disease, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *DLco* diffusing capacity of the lungs for carbon monoxide, *FVC* forced vital capacity, *DM* primary dermatomyositis, *COPD* chronic obstructive pulmonary disease, *ANA* antinuclear antibodies, *Anti-ARS* anti-aminoacyl transfer RNA synthetase

*$p < 0.001$, comparison between non-ILD and ILD

39; 37.5%), OP ($n = 7$; 6.7%), AIP (n = 4; 3.8%), and non-defined ($n = 9$; 8.6%). No relevant differences by types of ILD were detected in terms of clinical characteristics, antibody profile, or treatments (Online Resource Table S1).

Table 2 Interstitial lung disease patients: comparison according to subtype of idiopathic inflammatory myopathy

	PM ($N = 19$)	DM ($N = 18$)	ASS ($N = 50$)	OM ($N = 25$)
Female sex	11 (58%)	16 (89%)	38 (76%)	21 (84%)
Age at diagnosis (years)	60.9 (45.0–72.5)	55.2 (34.8–64.6)	52.2 (45.0–62.2)	42.7 (31.2–61.7)
Years from symptom to diagnosis	0.42 (0.10–1.12)	0.21 (0.07–0.37)	0.35 (0.17–2.51)	0.33 (0.14–3.08)
Baseline CK (U/L)	1690 (418–3200)	335 (200–1156)	1108 (221–5702)	651 (247–1996)
Baseline aldolase (U/L)	16.4 (8.4–40.0)	11.2 (4.4–27.0)	20.0 (12.0–30.0)	13.7 (8.8–33.6)
Maximum CRP in the first year (mg/dl)	1.4 (1.0–3.0)	6.0 (0.6–10.0)	4.0 (1.5–11.0)	5.0 (0.1–10.0)
Maximum ESR in the first year (mm/h)	49 (36–50)	44 (31–59)	46 (21–66)	69 (44–88)
DLco first year	71 (59–76)	59 (50–68)	66 (50–80)	65 (52–70)
FVC first year	70 (64–80)	62 (54–81)	72 (60–85)	70 (65–75)
Muscle weakness	18 (95%)	17 (94%)	46 (92%)	24 (96%)
Systemic manifestations	9 (47%)	13 (81%)	24 (50%)	15 (60%)
Arthritis/arthralgia*	7 (37%)	16 (89%)	42 (84%)	22 (88%)
Typical DM skin lesions				
Gottron papules*	–	14 (78%)	9 (18%)	3 (12%)
Heliotrope rash*	–	14 (78%)	6 (12%)	2 (8%)
Gottron sign*	–	15 (83%)	7 (14%)	2 (8%)
Cutaneous vasculitis	2 (10%)	1 (5%)	3 (6%)	3 (12%)
Cutaneous ulcers	1 (5%)	1 (6%)	–	2 (8%)
Ischemic ulcers	2 (10%)	1 (6%)	2 (4%)	8 (32%)
Periungual erythema	1 (5%)	6 (37%)	10 (20%)	6 (24%)
Mechanic's hands*	2 (10%)	11 (69%)	20 (40%)	4 (16%)
Calcinosis	1 (5%)	3 (17%)	2 (4%)	4 (16%)
Edema of hands	2 (10%)	7 (44%)	15 (30%)	16 (64%)
Raynaud's phenomenon	6 (31%)	5 (28%)	18 (36%)	20 (80%)
Sclerodactyly*	2 (10%)	–	7 (14%)	17 (68%)
Hematological manifestations	4 (21%)	4 (22%)	10 (20%)	10 (40%)
Dysphagia or reflux	7 (37%)	7 (39%)	9 (18%)	16 (64%)
Cardiac manifestations	12 (63%)	3 (17%)	10 (20%)	8 (32%)
Pulmonary hypertension	4 (21%)	–	11 (22%	7 (28%
Renal manifestations	1 (5%)	–	2 (4%)	3 (12%)
Subgroup of ILD				
UIP	8 (44%)	5 (38%)	19 (39%)	13 (54%)
NSIP	7 (39%)	2 (15%)	20 (41%)	10 (42%)
OP	1 (6%)	2 (15%)	4 (9%)	–
AIP	–	1 (8%)	3 (6%)	–
Not defined	2 (11%)	3 (23%)	3 (6%)	1 (4%)
Severe infections	7 (35%)	3 (18%)	11 (22%)	10 (48%)
Current smoking	2 (17%)	2 (25%)	7 (19%)	1 (8%)
Arterial hypertension	6 (31%)	5 (29%)	18 (36%)	12 (50%)
Diabetes mellitus	4 (21%)	1 (6%)	5 (10%)	2 (8%)
Pleurisy	–	–	1 (2%)	4 (17%)
COPD	3 (16%)	–	2 (4%)	–
Cardiovascular events	8 (42%)	1 (6%)	16 (32%)	10 (42%)
Dyslipidemia	9 (47%)	5 (29%)	20 (40%)	7 (29%)
Antibodies				
ANA	9 (47%)	12 (67%)	40 (80%)	23 (92%)
Anti-ARS*	–	–	50 (100%)	–
Anti-Ro*	–	–	22 (52%)	3 (16%)
Anti-RNP*	3 (16%)	1 (6%)	2 (4%)	11 (46%)

Muscle weakness was measured using the Medical Research Council scale. Data are presented as median and interquartile range (IQR) or *n* (%). Bonferroni correction was applied

PM primary polymyositis, *DM* primary dermatomyositis, *ASS* antisynthetase syndrome, *OM* overlap myositis, *CK* creatine kinase, *ILD* interstitial lung disease, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *DLco* diffusing capacity of the lungs for carbon monoxide, *FVC* forced vital capacity, *UIP* usual interstitial pneumonia, *NSIP* non-specific interstitial pneumonia, *OP* organizing pneumonia, *AIP* acute interstitial pneumonia, *COPD* chronic obstructive pulmonary disease, *ANA* antinuclear antibodies, *Anti-ARS* anti-aminoacyl transfer RNA synthetase

*$p < 0.001$, comparison between groups

Long-term poor prognostic outcomes

Mortality

A total of 32 deaths (29%) occurred during the follow-up period of 1061 patient-years up to a maximum of 35 years, achieving a survival probability of 50% after 29.8 years of follow-up. Data on the vital state of 8 patients, which were censored at the last visit, were not available. The 10-year survival probability by type of myositis was 74% for PM, 65.6% for DM, 73.6% for ASS, and 70.3% for OM, without differences in the survival function (Online Resource Fig. S1).

Table 3 Prognostic factors of mortality in idiopathic inflammatory myopathy associated with interstitial lung disease

	Bivariate HR [95% CI] (*p* value)	Multivariate HR [95% CI] (*p* value)
Female sex	0.77 [0.34–1.72] (0.525)	**0.19 [0.04–0.95] (0.044)**
Age at diagnosis (years)	**1.03 [1.01–1.06] (0.008)**	0.98 [0.94–1.01] (0.246)
Years from symptom to diagnosis	**1.11 [1.00–1.24] (0.045)**	**1.29 [1.06–1.56] (0.011)**
PM	1	
DM	0.81 [0.28–2.33] (0.694)	
ASS	0.68 [0.28–1.67] (0.400)	
OM	0.54 [0.19–1.57] (0.260)	
Baseline CK (U/L)	1.00 [1.00–1.00] (0.295)	
Baseline aldolase (U/L)	1.00 [0.98–1.02] (0.751)	
Maximum CRP in the first year (mg/dl)	0.99 [0.95–1.03] (0.661)	
Maximum ESR in the first year (mm/h)	**1.01 [1.00–1.03] (0.039)**	
DLco first year	0.22 [0.02–2.01] (0.179)	
CVF first year	**0.01 [0.005–0.27] (0.006)**	
Muscle weakness	2.06 [0.28–15.2] (0.477)	
Systemic manifestations	1.63 [0.76–3.49] (0.211)	
Arthritis/arthralgia	0.62 [0.27–1.43] (0.263)	
Gottron papules	0.84 [0.38–1.88] (0.675)	
Heliotrope rash	**2.42 [1.16–5.03] (0.018)**	**31.1 [3.41–283.6] (0.002)**
Gottron sign	0.97 [0.42–2.24] (0.941)	
Cutaneous vasculitis	1.32 [0.46–3.80] (0.603)	
Cutaneous ulcers	–	
Ischemic ulcers	0.77 [0.27–2.22] (0.629)	0.19 [0.02–1.54] (0.121)
Periungual erythema	0.67 [0.27–1.67] (0.390)	
Mechanic's hands	0.82 [0.37–1.81] (0.624)	
Calcinosis	0.20 [0.03–1.48] (0.115)	
Edema of hands or sclerodactyly	0.52 [0.24–1.11] (0.091)	
Raynaud's phenomenon	1.58 [0.77–3.25] (0.212)	**11.9 [1.98–71.20] (0.007)**
Hematological manifestations	1.72 [0.84–3.54] (0.138)	
Dysphagia or reflux	0.92 [0.44–1.90] (0.817)	
Cardiac manifestations	**2.18 [1.08–4.39] (0.030)**	4.67 [0.96–22.6] (0.055)
Renal manifestations	0.83 [0.19–3.63] (0.809)	
NSIP	1	
OP	0.41 [0.05–3.30] (0.401)	
UIP	1.23 [0.52–2.90] (0.628)	
AIP	**8.37 [3.12–33.04] (0.002)**	
Not defined ILD	0.53 [0.11–2.56] (0.431)	
CMP 3m	1.79 [0.82–3.91] (0.144)	**9.48 [1.98–45.32] (0.005)**
Severe infections	**4.84 [2.30–10.18] (<0.0001)**	**6.41 [1.41–29.1] (0.016)**
Current smoking	1.16 (0.34–4.00) (0.815)	1.17 [0.12–11.15] (0.889)
Ana+	0.56 [0.26–1.20] (0.135)	**0.08 [0.01–0.52] (0.008)**
Jo1+ vs. Ana+ and Jo1−	1.64 [0.70–3.82] (0.255)	
Jo1+ and Ro+ vs. Jo1+ and Ro−	0.88 [0.27–2.82] (0.829)	
Jo1+ vs. Jo1−	1.05 [0.51–2.17] (0.889)	
RNP− and Jo1− vs. RNP+ and Jo1−	1.40 [0.48–4.03] (0.531)	
RNP− and Jo1+ vs. RNP+ and Jo1+	–	
RNP− and Jo1+ vs. RNP+ and Jo1−	1.71 [0.55–5.32] (0.353)	
RNP+ vs. RNP−	0.65 [0.24–1.76] (0.397)	

Muscle weakness was measured using the Medical Research Council scale. The Harrell *C* statistic of the adjusted model was 89%

Data presented in bold text are statistically significant

PM primary polymyositis, *DM* primary dermatomyositis, *ASS* antisynthetase syndrome, *OM* overlap myositis, *CK* creatine kinase, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *DLco* diffusing capacity of the lungs for carbon monoxide, *FVC* forced vital capacity, *UIP* usual interstitial pneumonia, *NSIP* non-specific interstitial pneumonia, *OP* organizing pneumonia, *AIP* acute interstitial pneumonia, *CMP 3m* clinically meaningful progression in the first 3 months, *ANA* antinuclear antibodies

Regarding the type of ILD, the 10-year survival probability was 65% for UIP, 75.2% for NSIP, 100% for OP, 0% for AIP, and 85.7% for the non-defined, with significant differences in the survival function ($p = 0.001$). Highest and lowest mortality correlated with AIP and OP, respectively (Fig. 1). The main causes of death were cardiovascular event (10; 31%), ILD (9; 28%), infections (7; 22%), unknown causes (4; 12%), or other causes (2; 6%).

Necessity for long-term oxygen therapy

The total number of patients included in the survival analysis was 107, after excluding 5 patients from the initial sample (2 due to start of LTOT prior to IIM diagnosis, 2 due to an unknown start date, and 1 without LTOT and censored date). A total of 17 patients required LTOT (16%) during a 35-year maximum follow-up period with 967.8 patient-years.

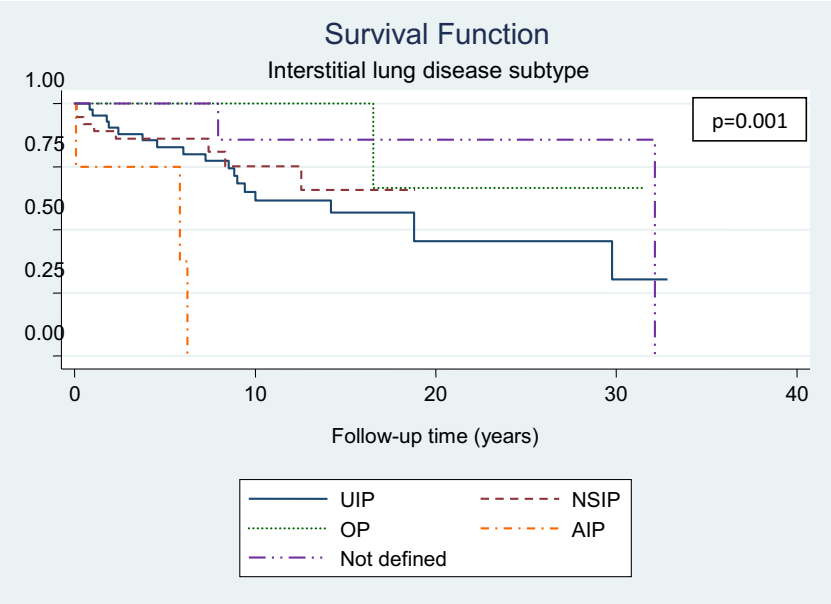

Fig. 1 Global mortality according to subtype of interstitial lung disease. UIP, usual interstitial pneumonia; NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia; AIP, acute interstitial pneumonia

Differences by type of myopathy ($p = 0.930$) or by type of ILD ($p = 0.112$) were not observed (Online Resource Figs. S2 and S3).

Deterioration of respiratory function tests

A total of 93 patients were included for survival analysis after excluding 19 patients from the initial sample (17 due to unavailable data on outcome measurement and 2 for presenting dates of last RFT determination that occurred prior to the dates of first determination). Deterioration of RFT occurred in 16 patients (17%) during a follow-up period of 36 years maximum with 581.5 patient-years, achieving a probability of deterioration in RFT of 25% after a 7-year follow-up period (25th percentile). Differences by type of myositis or type of ILD ($p > 0.05$) were not observed (Online Resource Figs. S4 and S5).

Prognostic factors

Mortality

Table 3 shows the results obtained in the bivariate analysis. In the multivariate model, being female (HR 0.19, 95% CI 0.04–0.95) and positivity only for ANA (HR 0.08, 95% CI 0.01–0.52) had protective effects. Severe infections (HR 6.41, 95% CI 1.41–29.1), the presence of heliotrope erythema (HR 31.1, 95% CI 3.41–283.6), a delay in diagnosis (HR 1.29, 95% CI 1.06–1.56), CMP 3m (HR 9.48, 95% CI 1.98–45.32), and RP (HR 11.9, 95% CI 1.98–71.2) were factors associated with mortality. These effects were independent of age at the time of diagnosis, active smoking habit, cardiac manifestations, and ischemic ulcers. The discrimination capacity of this final model for mortality was 89% (Table 3).

Necessity of long-term oxygen therapy

The results obtained from the bivariate analysis are shown in Table 4. In the multivariate model, the initial concentration of aldolase (HR 0.90, 95% CI 0.81–0.99) presented a protective effect, while CMP 3m (HR 22.7, 95% CI 1.43–360.72) was associated with the need for LTOT. These effects were independent of age at the time of diagnosis, ischemic ulcers, and maximum ESR level during year 1. The discrimination capacity of this model was 92% (Table 4).

Deterioration in respiratory function tests

Table 5 shows the results obtained from the bivariate analysis. The multivariate model showed that joint manifestations (HR 0.04, 95% CI 0.0–0.78) decreased with the risk of deterioration in RFT. This effect was independent of age at the time of diagnosis, active smoking habit, CRP during year 1, or ANAs. The discriminatory capacity of this model was 84% (Table 5).

Synthetic and biologic immunosuppressive agents and intravenous immunoglobulins did not contribute to the explanation of the three outcomes in the multivariate models.

Discussion

The results obtained in this retrospective multicentric study show the epidemiological, clinical, and immune differences between IIM with and without ILD. In turn, some differences were observed in profiles of antibodies and clinical

Table 4 Prognostic factors of long-term oxygen therapy in idiopathic inflammatory myopathy associated with interstitial lung disease

	Bivariate HR [95% CI] (*p* value)	Multivariate HR [95% CI] (*p* value)
Female sex	1.28 [0.37–4.45] (0.700)	
Age at diagnosis (years)	1.01 [0.98–1.04] (0.501)	1.05 [0.96–1.16] (0.270)
Years from symptom to diagnosis	1.12 [0.97–1.28] (0.113)	
PM	1	
DM	1.62 [0.27–9.73] (0.595)	
ASS	1.67 [0.35–7.87] (0.516)	
OM	1.48 [0.27–8.10] (0.649)	
Baseline CK (U/L)	1.00 [1.00–1.00] (0.137)	
Baseline aldolase (U/L)	0.93 [0.85–1.01] (0.080)	**0.90 [0.81–0.99] (0.049)**
Maximum CRP in the first year (mg/dl)	0.96 [0.88–1.05] (0.423)	
Maximum ESR in the first year (mm/h)	1.01 [0.99–1.03] (0.154)	1.03 [0.98–1.07] (0.216)
DLco first year	**0.02 [0.001–0.47] (0.014)**	0.10 [0.00–39.6] (0.454)
CVF first year	**0.01 [0.00–0.73] (0.035)**	
Muscle weakness	1.19 [0.16–8.99] (0.867)	
Systemic manifestations	0.92 [0.34–2.46] (0.873)	
Arthritis/arthralgia	0.85 [0.27–2.62] (0.777)	
Gottron papules	0.81 [0.26–2.49] (0.713)	
Heliotrope rash	1.38 [0.45–4.23] (0.575)	
Gottron sign	1.43 [0.50–4.07] (0.503)	
Cutaneous vasculitis	0.67 [0.09–5.06] (0.697)	
Cutaneous ulcers	–	
Ischemic ulcers	0.88 [0.20–3.88] (0.871)	10.58 [0.52–212.8] (0.124)
Periungual erythema	1.39 [0.49–3.97] (0.532)	
Mechanic's hands	1.01 [0.37–2.74] (0.979)	
Calcinosis	0.44 [0.06–3.37] (0.433)	
Edema of hands or sclerodactyly	0.86 [0.33–2.24] (0.761)	
Raynaud's phenomenon	0.97 [0.37–2.54] (0.945)	
Hematological manifestations	2.13 [0.81–5.60] (0.125)	
Dysphagia or reflux	1.25 [0.47–3.28] (0.654)	
Cardiac manifestations	1.36 [0.50–3.67] (0.548)	
Renal manifestations	2.34 [0.53–10.30] (0.259)	
NSIP	1	
OP	1.26 [0.25–6.27] (0.779)	
UIP	0.80 [0.27–2.39] (0.691)	
AIP	6.64 [0.75–58.4] (0.088)	
Not defined ILD	–	
CMP 3m	**2.80 [1.01–7.73] (0.045)**	**22.7 [1.43–360.72] (0.027)**
Severe infections	**2.62 [1.01–6.81] (0.047)**	
Current smoking	1.97 [0.41–9.59] (0.399)	
Ana+	1.45 [0.42–5.06] (0.557)	
Jo+ vs. Ana+ and Jo1−	1.30 [0.46–3.71] (0.623)	
Jo1+ and Ro+ vs. Jo1+ and Ro−	1.80 [0.33–9.85] (0.500)	
Jo1+ vs. Jo1−	1.16 [0.44–3.06] (0.756)	
RNP− and Jo1− vs. RNP+ and Jo1−	0.76 [0.20–2.94] (0.692)	
RNP− and Jo1+ vs. RNP+ and Jo1+	–	
RNP− and Jo1+ vs. RNP+ and Jo1−	1.27 [0.33–4.93] (0.726)	
RNP+ vs. RNP−	1.03 [0.29–3.75] (0.967)	

Muscle weakness was measured using the Medical Research Council scale. The Harrell *C* statistic of the adjusted model was 92%

Data presented in bold text are statistically significant

PM primary polymyositis, *DM* primary dermatomyositis, *ASS* antisynthetase syndrome, *OM* overlap myositis, *CK* creatine kinase, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *DLco* diffusing capacity of the lungs for carbon monoxide, *FVC* forced vital capacity, *UIP* usual interstitial pneumonia, *NSIP* non-specific interstitial pneumonia, *OP* organizing pneumonia, *AIP* acute interstitial pneumonia, *CMP 3m* clinically meaningful progression in the first 3 months, *ANA* antinuclear antibodies

characteristics in patients with IIM-ILD according to the type of myopathy but not according to the ILD pattern. On the other hand, although there were no differences in mortality, need for LTOT, or deterioration in RFT according to the type of myopathy, mortality was higher in AIP than in the rest of ILD. Severe infections, heliotrope erythema, delay in diagnosis, and RP were the main determinants of mortality risk. CMP 3m of ILD increased the risk both of mortality and the need for LTOT.

A recent meta-analysis of factors associated with ILD in IIM that included 23 studies [22] showed that delay in diagnosis, arthritis, acute phase reactants, constitutional syndrome,

Table 5 Prognostic factors of worsening in respiratory function tests in idiopathic inflammatory myopathy associated with interstitial lung disease

	Bivariate HR [95% CI] (*p* value)	Multivariate HR [95% CI] (*p* value)
Age at diagnosis (years)	1.00 [0.97–1.04] (0.794)	0.94 [0.87–1.02] (0.122)
Years from symptom to diagnosis	0.91 [0.70–1.19] (0.499)	
Female sex	1.24 [0.35–4.46] (0.736)	
PM	1	
DM	0.34 [0.07–1.71] (0.189)	
ASS	0.39 [0.12–1.25] (0.114)	
OM	0.30 [0.06–1.49] (0.141)	
Baseline CK (U/L)	1.00 [0.99–1.00] (0.701)	
Baseline aldolase (U/L)	0.99 [0.96–1.03] (0.676)	
Maximum CRP in the first year (mg/dl)	1.01 [0.95–1.07] (0.683)	1.04 [0.96–1.13] (0.365)
Maximum ESR in the first year (mm/h)	0.99 [0.96–1.01] (0.426)	
Muscle weakness	1.27 [0.16–9.67] (0.820)	
Systemic manifestations	1.30 [0.47–3.60] (0.610)	
Arthritis/arthralgia	**0.17 [0.05–0.51] (0.002)**	**0.04 [0.00–0.78] (0.034)**
Gottron papules	0.50 [0.14–1.78] (0.285)	
Heliotrope rash	1.39 [0.39–5.02] (0.609)	
Gottron sign	0.68 [0.19–2.41] (0.546)	
Cutaneous vasculitis	1.10 [0.14–8.48] (0.925)	
Cutaneous ulcers	–	
Ischemic ulcers	0.40 (0.05–3.23) (0.291)	
Periungual erythema	0.62 [0.17–2.21] (0.462)	
Mechanic's hands	1.16 [0.43–3.14] (0.755)	
Calcinosis	1.10 [0.25–4.91] (0.896)	
Edema of hands or sclerodactyly	0.65 [0.23–1.83] (0.413)	
Raynaud's phenomenon	0.73 [0.26–2.04] (0.551)	
Hematological manifestations	0.22 [0.03–1.70] (0.149)	
Dysphagia or reflux	1.22 [0.43–3.45] (0.706)	
Cardiac manifestations	1.25 [0.44–3.55] (0.669)	
Renal manifestations	–	
NSIP	1	
OP	–	
UIP	1.22 [0.37–4.04] (0.738)	
AIP	–	
Not defined ILD	0.41 [0.04–3.90] (0.437)	
CMP 3m	0.23 [0.05–1.02] (0.053)	
Severe infections	1.07 [0.34–3.38] (0.901)	
Current smoking	1.42 [0.29–6.92] (0.658)	1.61 [0.12–22.0] (0.723)
Ana+	**0.35 [0.13–0.93] (0.036)**	0.20 [0.03–1.17] (0.074)
Jo+ vs. Ana+ and Jo1−	1.45 [0.41–5.18] (0.559)	
Jo1+ and Ro+ vs. Jo1+ and Ro−	0.29 [0.03–2.47] (0.256)	
Jo1+ vs. Jo1−	0.88 [0.31–2.49] (0.819)	
RNP− and Jo1− vs. RNP+ and Jo1−	–	
RNP− and Jo1+ vs. RNP+ and Jo1+	–	
RNP− and Jo1+ vs. RNP+ and Jo1−	–	
RNP+ vs. RNP−	–	

Muscle weakness was measured using the Medical Research Council scale. The Harrell *C* statistic of the adjusted model was 84%

Data presented in bold text are statistically significant

PM primary polymyositis, *DM* primary dermatomyositis, *ASS* antisynthetase syndrome, *OM* overlap myositis, *CK* creatine kinase, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *DLco* diffusing capacity of the lungs for carbon monoxide, *FVC* forced vital capacity, *UIP* usual interstitial pneumonia, *NSIP* non-specific interstitial pneumonia, *OP* organizing pneumonia, *AIP* acute interstitial pneumonia, *CMP 3m* clinically meaningful progression in the first 3 months, *ANA* antinuclear antibodies

and the presence of anti-ARS antibodies are factors associated with ILD. These characteristics were present with higher frequency in our patients with ILD. Moreover, our results also revealed differences in other variables (RP, mechanic's hands, ischemic ulcers, edema of hands, and sclerodactyly) that were not analyzed in the meta-analysis and that are clinical features of ASS syndrome and OM (systemic sclerosis and mixed connective tissue disease). In the majority of studies that examined more than one type of myopathy, these were classified as PM, DM, and clinically amyopathic DM (CADM). The anti-ARS antibodies were associated with those subtypes, while in fewer studies, anti-MDA5 antibodies were also associated with them [5, 7, 8, 23–25]. In our analysis, all patients with anti-ARS antibodies and ILD are part of the same group;

therefore, the type of confusion caused by the presence of anti-ARS antibodies in every subtype of myopathy was eliminated. It is known that the pattern of ASS syndrome does not always include the presence of myositis [26]. In our study, due to REMICAM is a registry of myopathies, the majority of patients with ILD and ASS syndrome had myositis but also arthritis with or without other associated manifestations. Moreover, we studied OM because it can be associated with ILD and there is little available information on this form of IIM compared to the others. The classification of IIM used by Ober et al. is similar to that of our study [27]. However, these authors did not compare clinical characteristics by type of myopathy, and the OM group only included two patients. In our study, OM presented more sclerodactyly and anti-RNP antibodies since the majority of patients in this group had systemic sclerosis or mixed connective tissue disease.

There were no differences in the clinical characteristics according to type of ILD in our results. Furthermore, we did not found studies that carry out this type of analysis.

The survival probability by type of IIM was consistent with those already published, with a variation between 68 and 76.8% after 10 years for ASS and 82 and 71% in PM and DM, respectively, after 5 years [6, 7, 10, 11, 28]. It is being proven that anti-MDA5 antibodies are mainly detected in CADM [29, 30] and that these antibodies decrease survival, both in the short and long term, in patients with IIM-ILD [31, 32]. In our cohort, it was not possible to detect these antibodies, but the probability of a patient having them was low since no CADM was included. Therefore, our results suggest that survival among the various myopathies, including OM, is similar in the absence of CADM, which has been increasingly associated with anti-MDA5 antibodies [31, 32].

In previous studies that only included ASS, survival over time was analyzed by the type of ILD between UIP, NSIP, and OP and no differences were detected [11, 28, 33]. Our study encompassed different types of IIM, and the differences found can be explained by the inclusion of AIP, which is associated, as is already known, with high mortality [34].

Moghadam et al. reported that patients with ILD associated with DM, CADM, and anti-MDA5 suffered worse lung outcomes over time than patients without anti-MDA5 [6]. In our study, differences in lung outcomes (LTOT and RFT) analyzed by the type of myopathy or ILD were not detected over time. This is probably due to the fact that in this cohort there were no patients with anti-MDA5.

Our results are consistent with previously published poor prognostic factors such as RPLD, masculine gender, and low basal levels of muscle enzymes [7, 8, 10, 11, 24]. Likewise, we found that they are consistent with other published factors with protective effect such as arthritis. In this sense, it has been suggested that in ASS syndrome, non-Jo1 patients show less frequency of arthritis and a higher degree of pulmonary fibrosis than Jo1 patients [33]. In turn, we found that the presence of ANAs, without any other positive antibodies, had a protective effect. This effect would be explained, at least partially, because of the absence of anti-Pl7, anti-PL12, and anti-Ro antibodies that are related to a more severe pulmonary involvement [35, 36]. Previously, other authors and we reported that serious infections were associated with mortality in IIM [2, 37]. We support this suggestion in the present study focused on IIM associated with ILD. Our study also identified that delay in diagnosis, RP, and heliotrope erythema were risk factors of mortality that have not been described in patients with IIM and ILD. It is difficult to directly compare our results to previous data, since few studies exist that included these variables in their models, and they fundamentally analyzed patients with ASS syndrome [10, 11, 33]. When we review factors associated with mortality without distinguish between ILD or non-ILD patients, we find that delay in diagnosis has been associated with mortality [38]. Additionally, a study identified, by univariable analysis, RP associated with a higher risk of death in juvenile IIM patients [39]. On the other hand, some risk factors (RP, heliotrope erythema and CMP 3m) might be considered with precaution because of the great dispersion of the CI. For these reasons, these risk factors should be confirmed in other IIM-ILD cohorts. Distribution of synthetic and biologic immunosuppressive agents and intravenous immunoglobulins in each type of myositis was very homogenous and not contributed to explain prognosis models. During the last years, use of biologic immunosuppressive agents in IIM-ILD patients is more frequent, and probably results could be different in a current prospective cohort.

Our study has several limitations such as its retrospective design and the patient selection in tertiary hospitals, which could lead to a selection bias towards more severe forms of illness. The percentage of patients with UIP was higher than NSIP, which is in contrast with some published series of IIM and ILD [7, 10, 11, 27, 40]. Possible explanations could be the influence of OM with more UIP, patients with non-defined pattern, different radiologists assessing HRCT, and possible changes in the definition of patterns over time. Antibody detection was conducted in the laboratory of each hospital, not in a central laboratory, but antibodies were identified in the same way. As indicated above, anti-MDA5 could not be determined as it is not routinely available, although the odds of a particular patient being positive were lower since CADM was not included.

One of the study's strengths is that it is a multicentric cohort of IIM and the largest published in Spain to date, with a longer follow-up period than those reported in the majority of studies. This analysis provides information on Caucasian patients, while most studies have involved Asian patients. In addition, it utilizes a more appropriate method for classifying IIM than those previously used and adds information about patients with OM. Lastly, this study evaluates different poor prognostic outcomes, and not only mortality, which is generally the case.

In conclusion, the findings of this study deepen our understanding of IIM-ILD and can help identify patients with associated IIM and ILD based on their clinical characteristics. Additionally, information on long-term follow-up and poor prognostic outcomes has been expanded with our finding that the different types of IIM studied behave in similar ways as regards mortality, need for LTOT, and deterioration of RFT. We identified CMP 3m, severe infections, delay in diagnosis, heliotrope erythema, and RP as poor prognostic factors in different IIM associated with ILD. In our opinion, these results could be taken into account if they are confirmed, particularly in cases when an IIM patient has been diagnosed with ILD in order to identify the optimal treatment and to make any adjustments in accordance with the severity of the illness. Further prospective and multicentric studies in which patients are classified according to the presence of antibodies associated with ILD, such as anti-ARS and anti-MDA5, are needed in order to further confirm these results.

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Compliance with ethical standards

Disclosures None

Ethical approval

This study was approved by the ethics committees of the participant hospitals and carried out in compliance with the Helsinki Declaration.

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