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Interstitial lung disease and myositis-specific and associated autoantibodies: Clinical manifestations, survival and the performance of the new ATS/ERS criteria for interstitial pneumonia with autoimmune features (IPAF)

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ABSTRACT

Objective: to describe the clinical manifestations and survival of patients with ILD and myositis-specific and associated autoantibodies, and to evaluate the performance of the new ATS/ERS classification criteria for IPAF.

Patients and methods: Patients with ILD and positive in at least one of the following autoantibodies: anti-Jo-1, anti-Ej, anti-PL7, anti-PL 12, anti-PM/SCL 75 and anti-PM/SCL100 were included. Patients were separated into three groups according to their autoantibody profile: 1. Jo-1 positive patients, 2. Non-Jo-1 antisynthetase autoantibody positive patients, and 3. PM/SCL positive patients. Relevant clinical characteristics were registered. Patients were evaluated had they fulfilled Bohan and Peter's criteria (BPC) for inflammatory myopathies. We evaluated the performance of the IPAF ATS/ERS proposal to classify as such the patients that did not fulfilled BPC, and evaluated whether IPAF patients had a worse survival that BPC patients.

Results: Sixty-eight patients were included. Jo-1 was the most frequent autoantibody (65%), followed by non Jo1 anti-synthetase autoantibodies (31%). Non-Jo1 patients had lower Creatin Kinase serum levels at the baseline and less frequency of arthritis. Only 50% of patients fulfilled BPC. All patients not complying with BPC did comply with IPAF criteria. There was no difference in survival between IPAF and BPC patients. Anti Jo-1 positive was associated to survival and the extent of lung inflammation was associated to mortality.

Conclusions: Patients differ in clinical manifestations according to the autoantibody profile. All patients not complying with BPC did comply with the new IPAF criteria. There was no difference in survival between BPC and IPAF patients. Jo-1 patients had a better survival. Extent of lung inflammation was associate to mortality.

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1. Background

Patients being evaluated for interstitial lung disease (ILD) are a clinical diagnosis challenge. One clinical scenario is a patient presenting ILD and myositis-specific and associated autoantibodies. It has been described that many of these patients may have only subtle myositis clinical manifestations, and not comply with the Bohan & Peter [1–3] criteria (BPC) for an inflammatory myopathy

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[4]. To amend this, the ATS/ERS in 2015 proposed a new term: "interstitial pneumonia with autoimmune features" (IPAF) [5], in order to classify patients with suggestive features of a connective tissue disease but not complying with classification criteria for it. A patient with ILD may be classified as IPAF if he does not have an alternative diagnosis, does not meet classification criteria of a defined connective tissue disease and has at least one feature from at least two of the following domains: A. Clinical domain; B. Serological domain; and C. Morphological domain. Until now, the performance of the new IPAF ATS/ERS criteria, defined as the capacity of the new criteria to classify patients as such, in subjects with ILD and myositis-specific and associated autoantibodies not fulfilling BPC has not been evaluated. We also do not know whether survival is different in ILD patients fulfilling BPC compared to those classified as IPAF with myositis-specific and associated autoantibodies.

Recently, the availability of new diagnostic techniques that enable clinicians to detect autoantibodies that were only detected by immunoprecipitation [6], a laboratory technique available only in a few centers, has rapidly allowed the detection of patients with ILD as being positive for myositis-specific and associated autoantibodies such as anti-Jo1, anti-EJ, anti-OJ, anti-PL7, anti-PL12, anti PM/SCL 75, anti PM/SCL 100 and anti Ro52, among others autoantibodies. Antisynthetase autoantibodies (anti Jo-1, Anti Ej, anti Oj, anti PL7, anti PL12, among others) are associated to a specific clinical syndrome, the so-called antisynthetase syndrome. Nevertheless, the clinical manifestations of antisynthetase syndrome have been described in patients with other autoantibodies, such as anti PM/SCL [7,8]. Moreover, it seems that the serological profile in the antisynthetase syndrome is associated to survival, with non-Jo-1 patients having a worse survival compared to Jo-1 positive patients [9,10]. With this background, we wondered if patients with ILD and myositis-specific and associated autoantibodies overlapped in clinical manifestations, whatever the serological profile, and if these patients fulfilled BPC to be classified as an inflammatory myopathy, and in case they did not comply with BPC, we evaluated the performance of the new ATS/ERS classification criteria for IPAF [5] to classify patients as such. Finally, we evaluated if the serological profile and IPAF status is associated to survival.

2. Patients and methods

We included patients with ILD confirmed by high resolution chest tomography (HRCT), and positive in at least one of the following autoantibodies: anti-Jo1, anti-EJ, anti-OJ, anti-PL7, anti-PL12, anti PM/SCL 75, and anti PM/SCL 100; who were evaluated and treated at the interstitial lung disease and rheumatology unit, at the Instituto Nacional de Enfermedades Respiratorias, Ismael Cosio Villegas, a national tertiary care referral center for respiratory diseases, in Mexico City, between March 2006 and February 2015.

At baseline evaluation, all ILD patients are clinically evaluated by 1 of 4 pulmonologists and 1 rheumatologist seasoned in the evaluation of ILD. All patients are evaluated with pulmonary function tests which included the diffusing capacity of the lungs for carbon monoxide (DLCO), spirometry and plethysmography. Because of the pulmonary disease severity, some patients may have not be able to do these tests and this fact was described. Baseline laboratory values including serum creatin kinase level are obtained. All patients are evaluated with a broad serological panel searching for autoantibodies such as: antinuclear antibodies by immunofluorescence, anti DNAds, anti CCP, anti Ro, anti-La, anti RNP/SM, anti SM, anti Ro/SS-A, anti La/SS-B; anti SCL70, anti fibrillarin, anti Th/To, anti centromere, anti-Jo1, anti-EJ, anti-OJ, anti-PL7, anti-PL12, anti PM/SCL 75, anti PM/SCL 100, anti Ku and anti Ro52. The full description of the measurement of IgG myositis-specific and associated autoantibodies used in this manuscript may be found below.

We registered the following data from medical records or direct interview with patients or relatives: arthritis, Bohan and Peter myositis criteria, mechanic's hand sign (MH), fever, Raynaud's phenomenon, sclerodactyly, heliothrope rash, Gotron's papules and other dermatological signs related to dermatomyositis. A detailed description of the time elapsed between the onsets of respiratory and myositis symptoms until ILD diagnosis, drugs used to treat patients and clinical evolution, including time until death or follow up on the last visit time were obtained. The local institutional review board, named *comité de ciencia y bioética en investigación* (the science and bioethical research committee) in the INER, reviewed and approved the study protocol. All patients or relatives gave written informed consent to participate in the study.

2.1. Autoantibodies

The IgG myositis-specific and associated autoantibodies (Jo-1, PL7, PL12, Ej, Oj, PM/SCL75, PM/SCL 100) were measured using EUROIMMUN immunoblot strips (EUROLINE: Myositis profile 3) according to the manufacturer's instructions. Myosits Profile Euroline is a qualitative line immunoassay for the detection of human IgG autoantibodies. This commercial line blot assay for mysositis diagnosis was assessed on its diagnostic accuracy against RNA immunoprecipitation in a multicenter cohort of patients with IIM [6]. The overall specificity of the line blot is 92% compared to the 95% specificity of RNA immunoprecipitation. Sensitivity of the line blot is 38% compared to 43% of RNA immunoprecipitation. Concordance rate between the line blot and RNA immunoprecipitation is 91% [6].

3. High resolution chest tomography evaluation

HRCT was performed at baseline evaluation with a 1.0 or 1.5 mm thick axial section taken at 1 cm intervals throughout the entire thorax, and was reconstructed using a high-spatial frequency algorithm. Between 20 and 25 CT scan images were carried out for each patient. HRCT scans were evaluated by two experts blinded to clinical data (Mejia M and Mateos-Toledo H). Both readers evaluated the HRCTs independently, classifying the HRCT images according to the image pattern as either: 1) ground glass with consolidation images, with or without reticulation (organized pneumonia-like pattern); 2) ground glass and reticulation images without consolidation (nonspecific pneumonia-like pattern); and 3) basilar predominant reticulation, traction bronchiectasis and honeycombing with limited ground glass abnormality (usual pneumonia-like pattern) [11–14]. No other ILD HRCT pattern was found in this group of patients. All discrepancies were solved by consensus. The fibrotic component, defined by reticular opacities and inflammation by ground glass opacities, was graded according to the Kazerooni score [15] and the Goh score [16]. To evaluate the validity of this evaluation, the agreement between our two experts was evaluated using the intraclass correlation coefficient (ICC). In the case of the Kazerooni score the ICC between our two readers for fibrosis was 0.75 (95% CI: 0.53–0.87), and the ICC for ground glass opacities for the Kazerooni score was 0.72 (95% CI: 0.46–0.85). For the Goh score, the ICC was 0.73 (95% CI: 0.49–0.81) in the case of fibrosis. For ground glass opacities, the ICC was 0.90 (95% CI: 0.82–0.95). After the demonstration of good interobserver agreement, the scoring of one evaluator (Mejia M), (ICC of 0.90 (95% CI: 0.84–0.94 for intraobserver agreement) was used for further analysis in the comparison of patients who died and those who survived, or those who fulfilled BPC or not.

Table 1
Description of patients included in the study.

Variable	N: 68
Age (years old)	47.9 ± 10.69
Female sex	53 (78%)
Time between onset of symptoms and diagnosis, months	4 (2–12)
Jo1 positive patients	44 (65%)
Non-Jo1 patients	21 (31%)
Ej positive patients	10
PL 7	5
PL 12	7
Oj	1
PM/SCL positive patients	3 (4%)
PM/SCL 100	1
PM/SCL 75	3
Creatin kinase serum levels at baseline U/L	463 (87–1126.5)
Arthritis	45/63 (71.43%)
Fever	48 (70.5%)
Mechanic's hand sign	36/66 (54.5%)
Proximal muscle weakness	46/64 (72%)
Sclerodactyly/scleroderma	12/51 (23.5%)
Interstitial lung disease	68 (100%)
Ground glass and consolidation with or without reticulation (organized pneumonia like pattern)	39 (57.35%)
Ground glass, reticulation without consolidation (nonspecific interstitial pneumonia like pattern)	28 (41.18%)
Usual interstitial pneumonia like pattern	1 (1.47%)
Baseline % of predicted value of forced vital capacity (FVC)[a]	55.94 ± 22.41
Baseline % of predicted value of diffusing capacity of the lungs for carbon monoxide (DLCO)[b]	38.5 (30–76)

[a] Data from 61 patients, 7 patients were unable to perform spirometry because of the severity of lung disease.
[b] Data from 46 patients, DLCO is not recommended to be performed on patients with FVC <1 L. As for FVC, 22 patients were unable to perform DLCO because of the severity of lung disease or FVC <1 L.

4. Statistical analysis

A comparison of the frequency of signs and symptoms in baseline laboratory values, including creatin kinase levels and pulmonary function tests according to the serological profiles, was carried out. For this analysis we separated patients into three groups according to their autoantibody profile: 1. Jo-1 positive patients, 2. Non-Jo-1 antisynthetase autoantibody positive patients, and 3. PM/SCL positive patients. The comparison between these groups was done with one way anova or the Kruskall Wallis test as

Table 2
Comparison of clinical, laboratorial and extent of pulmonary disease evaluated with HRCT data in patients according serological profile, in patients with ILD and myositis-specific and associated autoantibodies.

Variable	Jo1 positive n:41	Non-Jo1 positive n:21	PM/SCL n: 3	P
Age at diagnosis	47 (40–56)	53.5 (44.5–60.5)	52 (48–54)	<0.23
Female sex	33 (75%)	18 (86%)	2 (66.6%)	<0.49
Time between onset of symptoms and diagnosis, months	3 (1–9)	12 (5–24)	4.5 (1–8)	<0.002[a]
Creatin kinase serum levels U/L	644 (237.5–2254)	124 (71–411)	655 (199–7460)	<0.004[b]
Proximal muscle weakness	33/42 (78.57%)	12/20 (60%)	1/2 (50%)	<0.17
Mechanic's hand sign	22/42 (52.4%)	12/21 (57.14%)	2/3 67%)	<0.91
Arthritis	33/39 (89%)	10/21 (60%)	2/3 (67%)	<0.008[c]
Fever	33/43 (80%)	12/21 (80%)	3/3 (100%)	<0.15
Raynaud's Phenomenon	10/29 (34%)	8/19 (42%)	1/3 (33.3%)	<0.89
Sclerodactyly/scleroderma	8/33 (24%)	4/17 (23.5)	0/3	<0.99
Gotron's papules/heliotrope rash	5/44 (11%)	3/21(14%)	0/3	<0.79
Organized pneumonia like pattern	25 (57%)	11 (52%)	3 (100%)	
Nonspecific interstitial pneumonia like pattern	19 (43%)	9 (43%)	0	<0.30
Usual interstitial pneumonia like pattern	0	1 (5%)	0	
Kazerooni ground glass score	2.6 (2.33–3)	2.33 (1.66–3)	3 (2.3–4.66)	<0.18
Kazerooni fibrosis score	0.33 (0–0.91)	1 (0.33–1.8)	0 (0–1)	<0.02[d]
Goh inflammation score	41.68 (34–52.71)	38.9 (23.5–52.08)	34 (25.76–83.84)	<0.69
Goh fibrosis score	2.72 (0.42–6.92)	5 (3.36–11.96)	2.24 (0–6.37)	<0.04[e]
Baseline % of predicted value of FVC	58 ± 24.5	51.63 ± 16.76	55.5 ± 33.2	<0.60
Baseline % of predicted value of DLCO	42 (30–77)	33 (22–54)	77 (77–77)	<0.36
Patients fulfilling IPAF criteria	18 (41%)	14 (67%)	2 (67%)	<0.094

[a] Comparison between non-Jo1 vs. Jo1 patients, $p < 0.0004$, considering a significance level of $p < 0.016$ according to the Bonferroni correction. There were no differences between Jo1 vs. PM/SCL or non-Jo1 vs, PM/SCL.
[b] Non-Jo1 patients had lower Creatin Kinase serum levels compared to Jo1 patients, $p < 0.001$, significance level of $p < 0.016$ according to the Bonferroni correction. There were no differences between Jo1 patients Vs PM/SCL and Non-Jo1 Vs PM/SCL.
[c] Exact Fisher test, no comparison between the groups is possible.
[d] Non-Jo1 patients showed a higher extent of pulmonary fibrosis than Jo1 patients when using the Kazerooni fibrosis score $P < .006$, significance level of $p < 0.016$ according to the Bonferroni correction. No differences were found between Jo1 vs. PM/SCL or non-Jo1 vs. PM/SCL.
[e] Non-Jo1 patients had a tendency towards a higher extent of pulmonary fibrosis compared to Jo1 positive patients when the Goh fibrosis score was used to measure the extent of fibrosis ($P < .019$, significance level of $p < 0.016$ according to the Bonferroni correction).

Table 3
Comparison among patients who fulfilled BPC and those patients who fulfilled IPAF criteria.

Variable	BPC n.34	IPAF n: 34	P
Age at diagnosis	46.64 ± 11.55	53.21 ± 9.32	<0.02
Female sex	27 (79.41%)	26 (76.47%)	<0.5
Time between onset of symptoms and diagnosis, months[a]	3.5 (1–10.5)	8 (3–18)	<0.03
Creatin kinase serum levels U/L[a]	843.5 (466–2837)	87 (47–256)	<0.001
Proximal muscle weakness	33 (97%)	13/30 (43.3)	<0.001
Mechanic's hand sign	21/33 (64%)	15/33 (45%)	<0.10
Arthritis	28/32 (87%)	17/31 (58%)	<0.005
Fever	29 (85%)	19/33 (58%)	<0.015
Raynaud's phenomenon	8/21 (38%)	11/30 (36.7%)	<0.99
Sclerodactyly/scleroderma	5/23 (21.7%)	7/28 (25%)	<0.99
Gotron's papules/heliotrope rash	7 (21%)	1 (3%)	<0.054
Organized pneumonia like pattern	22 (65%)	17 (50%)	
Nonspecific interstitial pneumonia like pattern	12 (35%)	16 (47%)	<0.32
Usual interstitial pneumonia like pattern		1 (3%)	
Kazerooni ground glass score[a]	2.6 (2.33–3)	2.5 (2.16–3)	<0.57
Kazerooni fibrosis score[a]	0 (0–0.5)	1 (0.33–1.33)	<0.006
Goh inflammation score[a]	44.2 (34–52.72)	38.64 (23.5–51.5)	<0.20
Goh fibrosis score[a]	2.56 (0–4.14)	5 (3.36–9.1)	<0.004
Baseline % of predicted value of FVC	59.54 ± 21.41	52.2 ± 23.16	<0.67
Baseline % of predicted value of DLCO	52.12 ± 26.86	43.59 ± 27.25	<0.94

[a] Median (IQR).

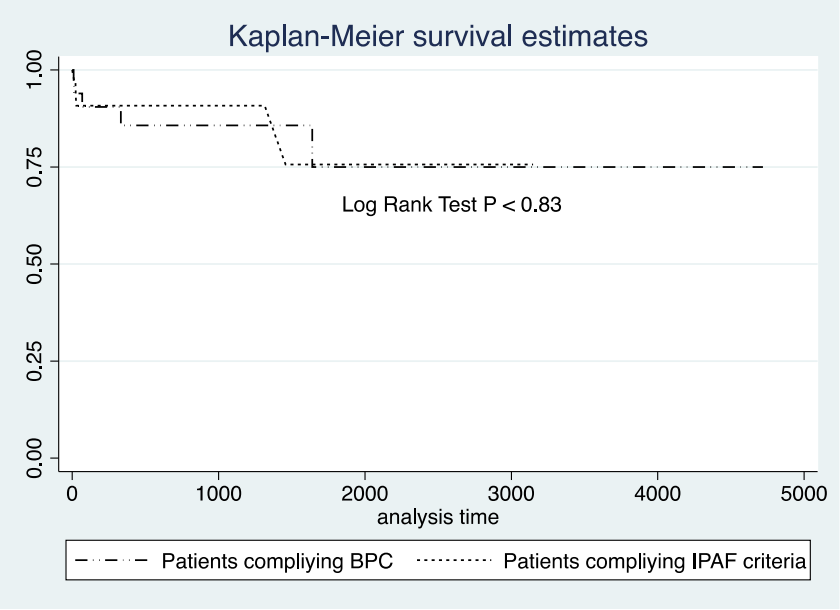

Fig. 1. There were no differences in survival between patients that comply BPC compared to patients that comply IPAF criteria.

appropriate. The comparison of specific groups was carried out, considering a significance level of $p < 0.016$ according to the Bonferroni Correction. Also, the degree of pulmonary disease was compared according to the serological profile. The survival function was estimated with the Kaplan Meier method. The differences in the survival function in the evaluated groups were compared with the log rank test. A univariate Cox regression analysis was performed to estimate the Hazard Ratio (HR) and its 95% confidence interval (95% CI) of the independent variables evaluated, in order to assess its association to time to death (dependent variable). Because of the small sample size, multivariable models with only two independent variables were elaborated to adjust for confounding in the variables associated to mortality.

5. Results

Sixty-eight patients with ILD and positive in at least one of the following autoantibodies: anti-Jo1, anti-EJ, anti-OJ, anti-PL7, anti-PL12, anti PM/SCL 75 and anti PM/SCL 100, were included. Ground glass and consolidation with or without reticulation (organized pneumonia like pattern) was the most frequent HRCT pattern, present in 57% of patients. The most prevalent autoantibody was Jo-1 in 41 patients (65%) followed by non-Jo-1 anti-ARS autoantibodies in 21 patients (31%), and 3 patients with PM/SCL autoantibodies (4%) (Table 1.) Fifty-three patients (78%) were female and the mean age of the sample at baseline evaluation was 49.83 ± 10.96. Fourteen Jo-1 positive patients were also positive to Ro52 and one Jo-1 patient was also positive to anti signal

recognition particle (anti-SRP) autoantibody. Some non-Jo-1 patients overlapped with other anti-synthetase.

or PM/SCL autoantibodies: Three Ej positive patients were also positive for anti-PL12, anti-PL7 and anti-Oj (one each); one anti-PL7 positive patient was also positive for anti PM/SCL 75, this patient was classified as a non-Jo-1 antisynthetase autoantibody positive patient in further analysis; Fourteen non-Jo-1 positive patients (67%) were also positive for anti-Ro52. The full description of the cohort may be found in Table 1.

5.1. Comparison of clinical manifestations according to the autoantibody profile

There were several differences among patients when compared according to the autoantibody profile (Table 2). Firstly, non-Jo1 patients had lower Creatin Kinase serum levels at the baseline, compared to Jo1 patients ($p < 0.001$, significance level of $p < 0.016$ according to the Bonferroni correction). Also, non-Jo-1 patients had less frequency of arthritis and finally, non-Jo1 patients showed a higher degree of pulmonary fibrosis than Jo1 patients when using the Kazerooni fibrosis score ($P < 0.006$, significance level of $p < 0.016$ according to the Bonferroni correction) and a tendency towards a higher degree of pulmonary fibrosis compared to Jo1 positive patients when the Goh fibrosis score was used ($P < 0.019$, significance level of $p < 0.016$ according to the Bonferroni correction). Finally, non-Jo1 patients had a delay in diagnosis of ILD compared to Jo1 patients (comparison between non-Jo1 vs. Jo1, $p < 0.0004$, considering a significance level of $p < 0.016$ according to the Bonferroni correction). Mechanic's hand sign was present in the three groups and no statistical difference was found ($P < 0.91$). There were no other differences in the frequency of fever, scleroderma or sclerodactyly, Gotron's papules or heliotrope rash between the three groups. PM/SCL patients did not differ with Jo1 and no Jo1 patients.

5.2. Performance of BPC for an inflammatory myopathy and the performance of the new criteria for IPAF

Only 34 patients (50%) fulfilled BPC to be classified as an inflammatory myopathy, (23 patients as possible polymyositis with 2 out of 4 criteria; 6 patients as probable polymyositis with 3 out of 4 criteria; and 5 with definitive dermatomyositis with typical rash of dermatomyosits plus any 3 of the other 4 criteria). All patients that did not fulfill BPC were classified as IPAF according to the ATS/ERS criteria proposal: Twenty-seven (79%) patients had at least one feature in each of the three IPAF domains and 7 (21%) patients had at least one feature in both serologic and morphologic domains. Table 3 describes the HRCT patterns of the morphologic domain. Moreover, four IPAF patients underwent pulmonary biopsy, 3 patients had nonspecific interstitial pneumonia and one patient had interstitial lymphoid aggregates with germinal centers.

There were no differences in survival between patients with BPC compared to IPAF criteria (Fig. 1). Nevertheless, BPC patients differed in many different ways to IPAF patients: IPAF patients were older at diagnosis and had more time between onset of symptoms and diagnosis (Table 3.) As may be expected, IPAF patients had less creatin kinase serum levels and less frequency of proximal muscle weakness. Also, IPAF patients had less arthritis and fever, as well as greater degrees of pulmonary fibrosis compared to BPC patients (Table 3.). We evaluated if the serological profile was associated with the IPAF classification and non Jo1 patients and PM/SCL patients had a tendency ($P < 0.094$) towards being more frequently classified as IPAF patients than as an inflammatory myopathy according BPC.

5.3. Comparison of survivors and non-survivors

The survival function at five years of follow up of the entire cohort was 75%. During follow up 9 patients died. Causes of death were the following: 4 patients due to sepsis, two patients died of myocardial infarction, 2 patients due to progressive respiratory

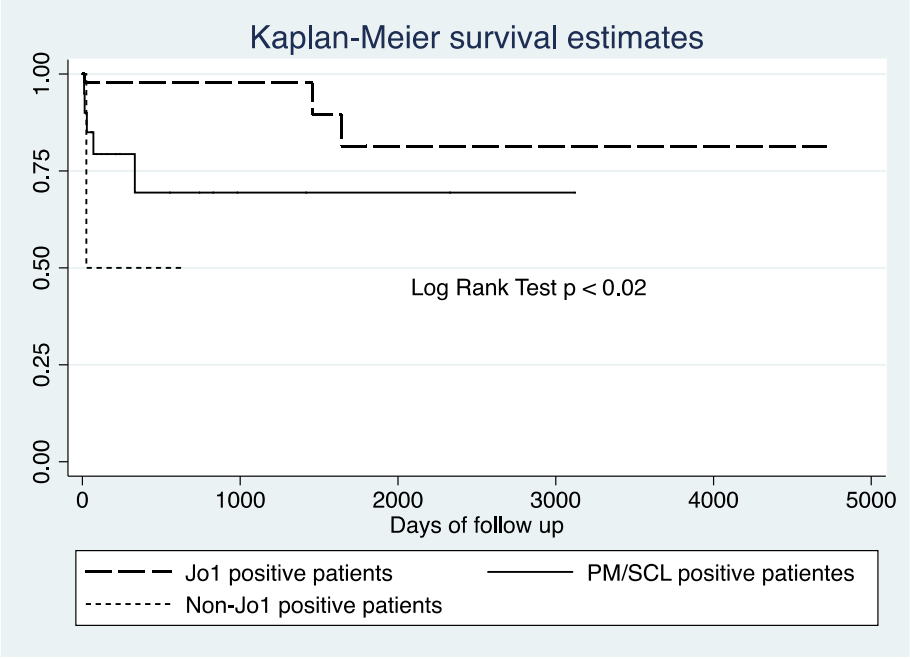

Fig. 2. Comparison of the survival function according the serological profile: Jo1 positive patients had better survival function compared to all other groups (Log Rank Test $P < 0.02$).

failure and one due to a stroke. Jo1 positive patients had better survival function compared to all other groups (Log Rank Test P < 0.02) (Fig. 2.). No differences in survival was found according to the HRCT pattern (Fig. 3A), even after adjusting for baseline % of predicted value of FVC (Fig. 3B) or baseline % of predicted value of DLCO (data not shown).

Table 4 displays the HR associated with mortality. There was a clear association between patients who were Jo 1 positive and better prognosis. (HR: 0.15, 95% CI: 0.04 - 0.58, P < 0.006). Age was associated to worse prognosis, and the presence of arthritis was associated to survival. The degree of inflammatory lung disease, measured both with the Goh score and the Kazerooni score, was clearly associated to worse survival. Ro52 positive patients did not have a worse prognosis compared to Ro52 negative patients (Log Rank Test < 0.82). To adjust for confounding, multivariable models were built with only two variables because of the small sample size (Table 5). In all evaluated models, Jo1 positivity was strongly associated to survival.

6. Discussion

In this single center cohort of ILD patients positive to at least one of the following autoantibodies: anti-Jo1, anti-EJ, anti-OJ, anti-PL7, anti-PL12, anti PM/SCL 75 and anti PM/SCL 100. We have found that

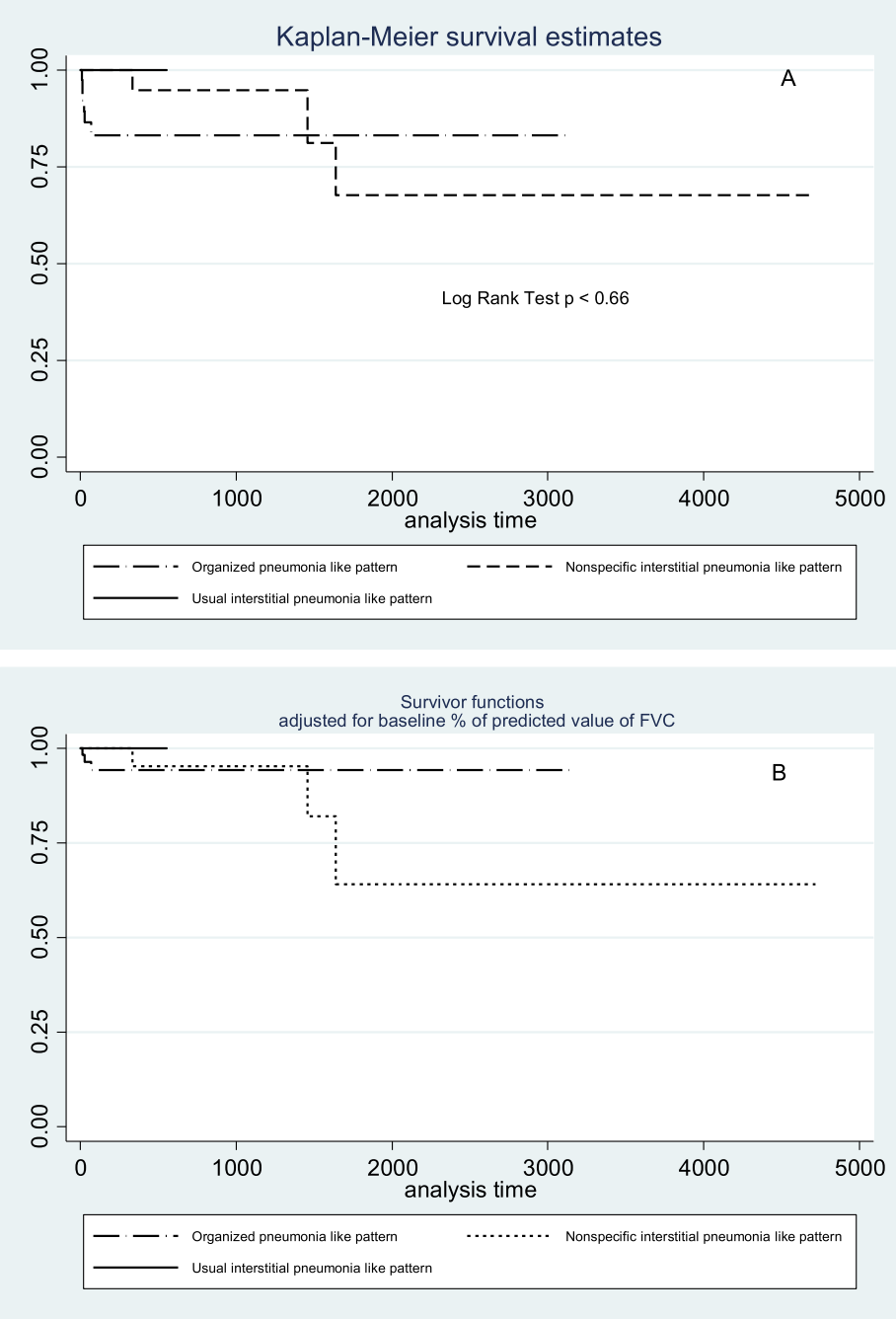

Fig. 3. A) Comparison of the survival function according to HRCT pattern. No differences were found. B) Comparison of the survival function according to HRCT pattern adjusted for baseline % of predicted value of FVC. The adjusted curves suggest there is no effect in survival according to HRCT pattern.

Table 4
Comparison among patients who died and those who survived.

Variable	Non-survivors 9 (13.24%)	Survivors 59 (86.76%)	HR (95% CI) P
Age at diagnosis	58.37 ± 11.64	48.65 ± 10.43	1.08 (1.01–1.16) <0.016
Time (months) between onset of symptoms and diagnosis[a]	3 (1–12)	5 (2–12)	0.97 (0.89–1.06) <0.60
Jo1 positivity	3 (30%)	39 (79.6%)	0.15 (0.04–0.58) <0.006
Creatine kinase serum levels at baseline U/L[a]	464 (352–723)	462 (80–1191)	0.99 (0.098–1.002) <0.51
Clinical evidence of muscle weakness	7/8 (87.5%)	39/56 (69.6%)	2.55 (0.31–20.8) <0.43
Arthritis	4 (44.4%)	41/54 (76%)	0.23 (0.06–0.89) <0.034
Fever	7 (78%)	41/58 (71%)	1.28(0.26–6.20) <0.75
Goh inflammation score[a]	52.08 (45–52.72)	40 (30.72–48)	1.04 (1.007–1.07) <0.02
Goh fibrosis score[a]	3.92 (2.16–6.37)	3.41 (1.74–7.36)	1.005 (0.93–1.08) <0.89
Kazerooni ground glass score[a]	3.16 (3–4)	2.5 (2.3–3)	3.79 (1.84–7.77) <0.0001
Kazerooni fibrosis score[a]	0.5 (0.33–1.3)	0.5 (0–1.16)	1.18 (0.54–2.56) <0.66
Forced vital capacity, % of expected[a]	44 (24–124)	73 (55–91.5)	0.98 (0.93–1.02) <0.39
Baseline % of predicted value of diffusing capacity of the lungs for carbon monoxide (DLCO)	48.5 (31–66.5)	38.5 (29–76.5)	0.94 (0.87–1.03) <0.22
Organized pneumonia like pattern	6 (67%)	33 (56%)	1.15 (0.23–5.8)[b] 0.85
Nonspecific interstitial pneumonia like pattern	3 (33%)	25 (42%)	1.51 (0.35–6.36)[c] 0.57
Usual interstitial pneumonia like pattern	0	1 (2%)	Not estimated[d]

[a] Median (IQR).
[b] The HR represents the time to an event risk of organized pneumonia like pattern patients compared to the other HRCT pattern patients.
[c] The HR represents the time to an event risk of nonspecific interstial pneumonia like pattern patients compared to the other HRCT pattern patients.
[d] The HR of usual interstitial pneumonia like pattern patients could not be estimated because there was only one patient with this HRCT pattern.

Table 5
Multivariable Cox regression models with two variables to adjust for confounding. In all evaluated models, Jo1 was associated to survival.

	Adjusted Hazard Ratios (95% CI)
Model 1	
Jo1 positivity	0.13 (0.02–0.75)
Goh inflammation score	1.06 (1.02–1.11)
Model 2	
Jo1 positivity	0.13 (0.02–0.77)
Kazerooni inflammation score	2.9 (1.56–5.41)
Model 3	
Jo1 positivity	0.19 (0.04–0.99)
Age at diagnosis	1.08 (1.01–1.17)
Model 4	
Jo1 positivity	0.07 (0.009–0.55)
Time (months) between onset of symptoms and diagnosis.	0.90 (0.78–1.04)

patients differ in clinical manifestations according to the autoantibody profile. Only 50% of the patients fulfilled BPC. However, those patients that did not fulfill BPC, were classified as IPAF. Hence, the new IPAF criteria had a good performance classifying patients as such. There was no difference in survival among BPC and IPAF patients. Jo-1 patients had a better survival and mortality was associated to the extent of lung inflammation.

As has been previously reported, patients with anti synthetase autoantibodies, differ clinically according to the serological profile [8]. In this cohort, non Jo1 patients had lower creatin kinase serum levels at the baseline, had less frequency of arthritis and finally, non-Jo1 patients showed a higher degree of pulmonary fibrosis than Jo1 patients. Also, as Aggarwal et al. [10] informed, non Jo1 patients had a delay in diagnosis compared to Jo1 patients. The lower prevalence of clinical manifestations, may explain why non jo1 patients had a delay in diagnosis compared to Jo1 patients. Another finding that this study seems to confirm [7,17], is that PM/SCL patients had clinical signs of the so called anti synthetase syndrome, such as mechanic's hands sign and arthritis. As clinicians treating with this group of patients, we believe that the serological evaluation in a patient with anti synthetase clinical features must include the evaluation of PM/SCL autoantibodies. It was revealing that one PL7 patient was also positive to PM/SCL 75 autoantibody. Our experience treating these patients is that PM/SCL positive patients have a very similar clinical condition to anti synthetase syndrome, and may have severe ILD and possible worse prognosis

than jo1 and non Jo1 positive patients. Nevertheless, we acknowledge that our experience is limited to a small number of PM/SCL positive patients.

In this study, the most prevalent autoantibody was Jo1 in 65% of the patients, very similar to what Aggarwal et al.[10] recently reported in an antisynthetase syndrome cohort, in which 60% of the patients were Jo1 positive. Jo1 has been consistently reported as the most prevalent of the antisynthetase autoantibodies [18,19]. As described elsewhere [9,10], Jo1 patients had better prognosis compared to non Jo1 patients. This report seems to confirm previous observations, nevertheless, there is some new data that should be discussed before concluding that Jo1 patients have better prognosis. Firstly, non-Jo1 patients had a delay in the diagnosis of ILD associated to myositis-specific or associated autoantibodies compared to Jo1 patients; and secondly non-o1 patients had a greater degree of pulmonary fibrosis. Although we adjusted for these confounders in the multivariable models evaluated, and no change in the original interpretation resulted, we cannot exclude that the delay in diagnosis for non-Jo1 patients results in a greater degree of pulmonary fibrosis and this may contribute to the worse survival of non-Jo1 patients. Non-Jo1 patients had other clinical differences to Jo1 patients: they had lower levels of creatin kinase serum levels and less frequency of arthritis. These differences may result in a delay in the time between onset of symptoms and diagnosis. Another factor that has been related to worse prognosis or more severe disease in ASS patients is the positivity to Ro52 autoantibody [20,21]. In our study, there was no difference in survival according to anti Ro52 status.

Our report is one of the first to evaluate the performance of the new ATS/ERS proposal of IPAF, in a population of ILD patients that do not fulfill BPC however positive to autoantibodies specific and associated to myositis. The new IPAF criteria had a good performance in the capacity to classify as such patients not fulfilling BPC. It was quite shocking to discover that only 50% of the patients in this cohort could be classified as an inflammatory myopathy according BPC. Although not statistically significant, non-Jo1 patients and PM/SCL patients were more frequently classified as IPAF patients (67% each) than Jo1 patients (41%). As expected, there were several differences between BPC patients and IPAF patients, mainly related to myositis manifestations. Interestingly, no difference in survival was observed between IPAF and BPC patients, this lack of difference in survival may be explained because there were no differences in the extent of inflammation or the pulmonary function tests between IPAF and BPC patients. Although, IPAF patients had higher extent of pulmonary fibrosis, this difference seems clinically not relevant and did not reflect any difference in the FVC and DLCO values of the patients. Moreover, neither group reached the fibrosis scores associated with mortality in ILD patients [15,22,23].

Our study has several limitations; the first one is the sample size. The small sample size is the reason why we only could adjust for confounding with only two variables. Another limitation regarding the evaluation of the IPAF criteria is that we restricted our analysis to a limited number of autoantibodies rather than the full range of autoantibodies considered in the IPAF criteria. Moreover, in our institution we do not have access to anti MDA-5 autoantibodies, which have been related to severe ILD. Nevertheless, we believe that our study contributes with relevant clinical information.

In conclusion, patients differ in clinical manifestations according to the autoantibody profile, with non Jo1 patients having less frequency of arthritis and lower levels of creatin kinase at baseline. The new IPAF criteria had good performance in classifying as such patients that did not fulfill BPC and there was no difference in survival among BPC and IPAF patients. Jo-1 patients had a better survival and mortality was associated to the extent of lung inflammation.

Conflict of interest

None.

References

[1] A. Bohan, J.B. Peter, Polymyositis and dermatomyositis (second of two parts), N. Engl. J. Med. 292 (8) (1975) 403–407.
[2] A. Bohan, J.B. Peter, Polymyositis and dermatomyositis (first of two parts), N. Engl. J. Med. 292 (7) (1975) 344–347.
[3] A. Fischer, S.G. West, J.J. Swigris, K.K. Brown, R.M. du Bois, Connective tissue disease-associated interstitial lung disease: a call for clarification, Chest 138 (2) (2010) 251–256.
[4] V. Cottin, Interstitial lung disease: are we missing formes frustes of connective tissue disease? Eur. Respir. J. 28 (5) (2006) 893–896.
[5] A. Fischer, K.M. Antoniou, K.K. Brown, et al., An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features, Eur. Respir. J. 46 (4) (2015) 976–987.
[6] A. Ghirardello, M. Rampudda, L. Ekholm, et al., Diagnostic performance and validation of autoantibody testing in myositis by a commercial line blot assay, Rheumatol. Oxf. 49 (12) (2010) 2370–2374.
[7] J.C. Lega, V. Cottin, N. Fabien, F. Thivolet-Bejui, J.F. Cordier, Interstitial lung disease associated with anti-PM/Scl or anti-aminoacyl-tRNA synthetase autoantibodies: a similar condition? J. Rheumatol. 37 (5) (2010) 1000–1009.
[8] J.C. Lega, N. Fabien, Q. Reynaud, et al., The clinical phenotype associated with myositis-specific and associated autoantibodies: a meta-analysis revisiting the so-called antisynthetase syndrome, Autoimmun. Rev. 13 (9) (2014 Sep) 883–891.
[9] J. Rojas-Serrano, D. Herrera-Bringas, M. Mejia, H. Rivero, H. Mateos-Toledo, J.E. Figueroa, Prognostic factors in a cohort of antisynthetase syndrome (ASS): serologic profile is associated with mortality in patients with interstitial lung disease (ILD), Clin. Rheumatol. 34 (9) (2015) 1563–1569.
[10] R. Aggarwal, E. Cassidy, N. Fertig, et al., Patients with non-Jo-1 anti-tRNA-synthetase autoantibodies have worse survival than Jo-1 positive patients, Ann. rheumatic Dis. 73 (1) (2014) 227–232.
[11] T. Mimori, R. Nakashima, Y. Hosono, Interstitial lung disease in myositis: clinical subsets, biomarkers, and treatment, Curr. Rheumatol. Rep. 14 (3) (2012) 264–274.
[12] W.D. Travis, U. Costabel, D.M. Hansell, et al., An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias, Am. J. Respir. Crit. Care Med. 188 (6) (2013) 733–748.
[13] D.M. Hansell, A.A. Bankier, H. MacMahon, T.C. McLoud, N.L. Muller, J. Remy, Fleischner Society: glossary of terms for thoracic imaging, Radiology 246 (3) (2008) 697–722.
[14] M. Kalluri, C.V. Oddis, Pulmonary manifestations of the idiopathic inflammatory myopathies, Clin. Chest Med. 31 (3) (2010) 501–512.
[15] E.A. Kazerooni, F.J. Martinez, A. Flint, et al., Thin-section CT obtained at 10-mm increments versus limited three-level thin-section CT for idiopathic pulmonary fibrosis: correlation with pathologic scoring, AJR AmJRoentgenol 169 (4) (1997) 977–983.
[16] N.S. Goh, S.R. Desai, S. Veeraraghavan, et al., Interstitial lung disease in systemic sclerosis: a simple staging system, Am. J. Respir. Crit. Care Med. 177 (11) (2008) 1248–1254.
[17] I. Marie, L. Lahaxe, O. Benveniste, et al., Long-term outcome of patients with polymyositis/dermatomyositis and anti-PM-Scl antibody, Br. J. Dermatol. 162 (2) (2010) 337–344.
[18] Z.E. Betteridge, H. Gunawardena, N.J. McHugh, Novel autoantibodies and clinical phenotypes in adult and juvenile myositis, Arthritis Res. Ther. 13 (2) (2011) 209.
[19] H. Gunawardena, Z.E. Betteridge, N.J. McHugh, Newly identified autoantibodies: relationship to idiopathic inflammatory myopathy subsets and pathogenesis, Curr. Opin. Rheumatol. 20 (6) (2008) 675–680.
[20] I. Marie, P.Y. Hatron, S. Dominique, et al., Short-term and long-term outcome of anti-Jo1-positive patients with anti-Ro52 antibody, Semin. Arthritis Rheum. 41 (6) (2012) 890–899.
[21] J. Bauhammer, N. Blank, R. Max, et al., Rituximab in the treatment of Jo1 antibody-associated antisynthetase syndrome: anti-Ro52 positivity as a marker for severity and treatment response, J. Rheumatol. (2016).
[22] C.A. Kelly, V. Saravanan, M. Nisar, et al., Rheumatoid arthritis-related interstitial lung disease: associations, prognostic factors and physiological and radiological characteristics—a large multicentre UK study, Rheumatol. Oxf. 53 (9) (2014) 1676–1682.
[23] S.E. Gay, E.A. Kazerooni, G.B. Toews, et al., Idiopathic pulmonary fibrosis: predicting response to therapy and survival, AmJRespirCrit Care Med. 157 (4 Pt 1) (1998) 1063–1072.