RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Interstitial lung disease with and without progressive fibrosing phenotype in patients with idiopathic inflammatory myopathies: data from a large multicentric cohort

Elisabetta Zanatta ,[1] Elisabetta Cocconcelli,[2] Gioele Castelli ,[2] Chiara Giraudo,[3] Anna Sara Fraia,[3] Elena De Zorzi,[2] Mariele Gatto,[1] Luana Ienna,[1] Elena Treppo,[4] Danilo Malandrino,[5] Lorenzo Cereser,[6] Giacomo Emmi ,[5,7] Federico Giannelli,[8] Serena Bellani,[2] Andrea Martini,[9] Beatrice Moccaldi,[1] Anna Ghirardello,[1] Jérôme Avouac,[10] Luca Quartuccio ,[4] Yannick Allanore,[10] Andrea Doria ,[1] Paolo Spagnolo,[2] Elisabetta Balestro,[2] Luca Iaccarino[1]

To cite: Zanatta E, Cocconcelli E, Castelli G, *et al*. Interstitial lung disease with and without progressive fibrosing phenotype in patients with idiopathic inflammatory myopathies: data from a large multicentric cohort. *RMD Open* 2023;**9**:e003121. doi:10.1136/rmdopen-2023-003121

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/rmdopen-2023-003121).

EZ and EC contributed equally.
EB and Lla contributed equally.

EZ and EC are joint first authors.
EB and Lla are joint senior authors.

Received 2 March 2023
Accepted 17 July 2023

For numbered affiliations see end of article.

Correspondence to
Dr Andrea Doria;
adoria@unipd.it

ABSTRACT

Objectives Patients with connective tissue diseases can develop interstitial lung disease (ILD), leading to a progressive fibrosing ILD (PF-ILD) phenotype in some cases. We aimed to investigate the occurrence of PF-ILD in idiopathic inflammatory myopathies (IIMs), and factors potentially predicting this phenotype. Secondary aims were to assess the radiological pattern and factors associated with IIMs-ILD.

Methods Patients with IIMs from our multicentric prospective cohort were retrospectively evaluated. Data were recorded at IIMs and ILD diagnosis, and during follow-up. Patients with ILD were classified according to the predominant high-resolution CT (HRCT) pattern: non-specific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP) and organising pneumonia (OP). PF-ILD was defined according to the 2022 American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS) and Latin American Thoracic Society (ALAT) guidelines. Univariate and multivariate analyses were performed to identify factors associated to ILD and to PF-ILD.

Results Of 253 patients with IIMs, 125 (49%) had ILD: 99 (78%) at IIMs diagnosis and 26 (22%) during follow-up (21/26 within 5 years). Multivariate analysis identified anti-Jo-1, anti-MDA5, anti-Ro52, high score on manual muscle test, mechanic's hands and Raynaud's phenomenon as independently associated with ILD. The predominant HRCT pattern was NSIP (50% of patients), followed by UIP (28%) and OP (22%). At 1-year follow-up, PF-ILD occurred in 18% of IIMs-ILD. PF-ILD was predicted by anti-MDA5, heliotropic rash, xerostomia and xerophthalmia at univariate but not at multivariate analysis.

Conclusion Patients with IIM should be carefully screened for ILD at IIMs diagnosis and yearly during follow-up. All patients with IIMs-ILD should be carefully monitored to capture ILD progression since a consistent proportion of them are expected to develop PF-ILD.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with connective tissue diseases (CTDs) may develop progressive fibrosing interstitial lung disease (PF-ILD). Among patients with idiopathic inflammatory myopathies (IIMs), ILD is detectable in up to 50% of cases. However, unlike in other CTDs (eg, systemic sclerosis, rheumatoid arthritis), the occurrence of PF-ILD has been poorly investigated in patients with IIMs.

WHAT THIS STUDY ADDS

⇒ This study provides real-life data on the occurrence of PF-ILD in a large multicentre cohort of patients with IIMs. The reported association between different radiological patterns and clinical/serological features may allow a better stratification of patients with IIMs in different clinical phenotypes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings suggest that clinicians ought to carefully monitor patients with IIMs-ILD for ILD progression. The considerable proportion of patients with IIMs who develop PF-ILD highlights the importance of future research to better define the treatment of these patients, especially the potential role of antifibrotics.

INTRODUCTION

Interstitial lung disease (ILD) can be observed in up to 50% of patients with idiopathic inflammatory myopathies (IIMs).[1] Although this rate is similar to that observed in systemic sclerosis (SSc)—wherein experts agree to perform high-resolution CT (HRCT) of the lung at SSc diagnosis and pulmonary function

tests (PFTs) at least yearly—to date there is no consensual screening strategy for ILD in IIMs.[2 3] Nevertheless, early and timely detection of IIMs-ILD is of the utmost importance, as ILD may require a close follow-up and tailored treatment approach.

The ILD radiological pattern may differ among patients with IIMs. The most common HRCT feature is the non-specific interstitial pneumonia (NSIP), followed by organising pneumonia (OP), and usual interstitial pneumonia (UIP).[4] Notably, recent studies have highlighted that all patients with ILD, not only those with idiopathic pulmonary fibrosis (IPF), can potentially develop a progressive fibrosing ILD (PF-ILD).[5–7] PF-ILD is a self-sustaining process which is identified based on radiological, clinical and functional decline features and may occur at any time during follow-up (ie, in prevalent ILD cases).[8] Data from nine centres across the UK showed that patients with PF-ILD have a significantly higher mortality compared with those with non-PF-ILD, and similar to patients with IPF who are characterised by particularly poor prognosis.[9] Early identification of predictors of PF-ILD may help improve patient management (eg, adopting a more aggressive therapeutic strategy in earlier stages of IIMs-ILD) and prognosis. Moreover, there has been growing interest for the study of PF-ILD in connective tissue diseases (CTDs) after the INBUILD trial results showed the efficacy of nintedanib—a tyrosine-kinase inhibitor—in reducing the rate of forced vital capacity (FVC) decline versus placebo in patients with PF-ILD related to rheumatic systemic diseases.[10] Although only two patients with IIMs were included in this randomized clinical trial (RCT), recent evidence[11 12] suggests that patients with IIMs may develop PF-ILD not unlike patients with other CTDs (eg, SSc or rheumatoid arthritis). However, its occurrence has been poorly investigated so far in IIMs-ILD.

The primary aim of our study was to assess the prevalence and predictors of PF-ILD in a large, multicentre cohort of patients with IIM-ILD. Secondary aims were to explore clinical and serological features associated with ILD occurrence in IIMs, and the association between different chest HRCT patterns and clinical-functional data of patients with IIMs-ILD.

METHODS

Study population

We conducted a retrospective cohort study comprising consecutive patients affected by IIMs—according to Bohan and Peter's criteria, the European Neuromuscolar Center (ENMC) criteria or 2017 EULAR/ACR classification criteria[13–15] followed-up in four third-level referral centres (Padova, Firenze, Udine, and Paris-Cochin Rhumatologie)[15] between 2002 and 2020. Enrolled patients had to have at least one visit with PFTs, after the diagnosis of IIMs. Exclusion criteria were: juvenile idiopathic inflammatory myopathies (ie, IIM diagnosis at <18 years), incomplete and/or unavailable clinical and/or serological baseline data, myositis in other CTDs, unavailable follow-up visits.

The following demographic, clinical and laboratory variables were collected at diagnosis and every year during the follow-up: constitutional symptoms (fever, asthenia and weight loss); articular involvement (arthritis and/or inflammatory arthralgia); muscular involvement (myalgia, muscular weakness, dyspnoea and dysphagia); skin manifestations (eg, Gottron's papules and signs, mechanic's hands) and other manifestations, including Raynaud's phenomenon (RP), xerostomia and xerophthalmia. All patients underwent manual muscle test 8 (MMT-8), PFTs including total lung capacity, FVC and diffusing capacity for carbon monoxide (DLCO), serum levels of creatine kinase (CK), lactate dehydrogenase and myoglobin. PFTs were recorded at diagnosis and yearly during follow-up. All patients were screened for ILD by medical evaluation (eg, bibasilar crackles), PFTs and/or X-rays. When ILD was suspected due to abnormal signs during clinical examination or imaging findings, HRCT was performed.

Further diagnostic investigations—that is, muscle MRI and/or electromyography and/or muscle biopsy—were performed according to the physician's judgement.

Autoantibody evaluation

Autoantibodies were tested in all patients at diagnosis: serum anti-nuclear antibodies were analysed by immunofluorescence assay on HEp-2 cells, anti-extractable nuclear antigen antibodies by ELISA and immunoblot, myositis specific autoantibodies (MSA) and myosistis associated autoantibodies (MAA) by commercial line blots (*Euroline Myositis Profile, Euroimmun, Lubeck, Germany*) including recombinant human proteins for Mi-2 alpha, transcription intermediary factor 1-gamma, small ubiquitin-like modifier-1 activating enzyme, Ku, PM-Scl75/100, MDA-5, signal recognition particle, Jo-1, PL-7, PL-12, EJ, and OJ.[16]

Comparison between patients with and without ILD and radiological evaluation in patients with IIMs-ILD

The diagnosis of ILD was based on HRCT. Clinical and serological data at IIM diagnosis were compared between IIM-non-ILD and IIM-ILD population. As some patients developed lung involvement during follow-up and not at the time of IIM diagnosis, we also compared clinical and serological data between IIM non-ILD population, patients with ILD at IIM diagnosis and those who developed ILD during follow-up.

Patients with fully available imaging for review were evaluated by four experienced thoracic radiologists (CG, LC, FG, AF) and classified into three subgroups according to the predominant radiological pattern: NSIP as group 1; UIP (definite and probable according to the latest guidelines[17]) as group 2; and OP, as group 3. The same IIM-ILD population was also grouped based on the three main IIM clinical phenotypes: polymyositis (PM), dermatomyositis (DM) and antisynthetase syndrome (ASyS). The three radiological subgroups (NISP, UIP

and OP) were compared considering clinical, functional and serological data collected at the time of IIMs-ILD diagnosis, and differences in predominant radiological features among the main IIMs clinical phenotype were analysed.

Identification of patients with progressive fibrosing IIM-ILD

Patients with IIM-ILD were further subgrouped in progressors (PF-ILD) and not-progressors (non-PF-ILD) according to the latest definition of PF-ILD provided by the 2022 ATS/ERS/JRS/ALAT guidelines.[17] More specifically, patients displaying at least two of the following three characteristics in the first year after IIMs-ILD diagnosis were classified as PF-ILD: (1) worsening of respiratory symptoms; (2) functional deterioration (defined by an absolute decline in FVC of more than 5% and in DLCO (adjusted for haemoglobin) of more than 10% within 1 year of follow-up); and (3) radiological worsening (identified as the increased extent of traction bronchiectasis, reticular abnormality, honeycombing, a new ground-glass opacity and increased lobar volume loss). Among patients with IIM-ILD, only those with functional and/or radiological data at ILD diagnosis and after 1-year follow-up were included in the evaluation of progression.

Clinical, functional and serological features at the time of IIM-ILD diagnosis were also compared between patients with PF-ILD and non-PF-ILD. Finally, we evaluated the immunosuppressive pharmacological treatment during the first year after IIMs-ILD diagnosis to explore potential differences between the two groups.

Ethics statement

This was a retrospective study on anonymised patient data collected from medical records. The study protocol was in accordance with current national regulation on retrospective observational studies.

Statistical analysis

Continuous variables were expressed as mean±SD or median (25th–75th IQR) and categorical variables as frequencies and percentages. Comparisons between groups were performed using the Mann-Whitney U test for continuous variables and the χ^2 test or Fisher's exact probability test for categorical data, where appropriate. Variables which were found to be different ($p<0.1$) between patients with and without ILD, and between PF-ILD and non-PF-ILD at univariable analysis were included in a multivariable logistic regression model, adjusted for age and sex. Two-sided $p<0.05$ was considered statistically significant. Kaplan-Meier survival analysis was performed to assess ILD-free survival in the subgroup of patients who developed ILD during follow-up. The statistical analysis was performed using the SPSS statistical package, V.22.0.

RESULTS

Demographic and clinical characteristics of the study population

Two hundred and fifty-three patients affected with IIMs were included in the study: 183 (72%) women, median age at diagnosis 55 (IQR 46–66) years. Among the overall population, a total of 125/253 (49.4%) patients exhibit ILD (figure 1): 99/125 (79%) had ILD at IIMs diagnosis and 26/125 (21%) developed ILD during follow-up. Baseline demographic characteristics of the study population are reported in table 1. The median follow-up (range) was 6 (3–10) years and was comparable in patients with and without ILD (p=0.44). Considering IIMs clinical phenotype (table 1), most patients were diagnosed as DM (96/253, 38%), followed by ASyS (77/253, 30%) and PM (67/253, 27%). The remaining IIM clinical phenotypes necrotizing autoimmune myopaty (NAM) and inclusion body myositis (IBM) were found exclusively in patients without ILD. Nine patients (3.5%), all with positive PM-Scl antibodies, had an overlap syndrome with SSc.

Evaluation of factors associated with ILD

Serological and clinical features, and treatment in patients with and without ILD

Among patients who exhibited ILD during the follow-up, 21 out of 26 (81%) developed ILD within the first 5 years from IIMs diagnosis (online supplemental figure 1).

Compared with patients with ILD at IIM diagnosis, those who developed ILD during follow-up showed similar baseline demographic, serological and clinical variables (online supplemental table 1), with a similar follow-up period in the two groups (p=0.19).

In patients developing ILD (either at IIM diagnosis or during follow-up) anti-Jo1 ($p<0.0001$), anti-SSA/Ro ($p<0.0001$), anti-Ro52 (p=0.0002) and anti-MDA5 (p=0.01) were more frequently found in patients with IIMs with ILD than in those without (table 1). By contrast, anti-Mi 2 was more frequently detected in patients without ILD (p=0.005). In patients without ILD, CK values were higher (p=0.001), MMT-8 score was lower ($p<0.0001$) and histological and/or MRI features of myositis were more frequent ($p<0.0001$) than in those with ILD. Patients with ILD more frequently had fever (p=0.004), arthritis (p=0.0003), RP (p=0.02) and mechanic's hands ($p<0.0001$). (table 1). Glucocorticoids were taken by the same proportion of patients in the two groups, although at lower dosage in patients with ILD compared with those without. Patients without ILD were more frequently treated with methotrexate and high-dose intravenous immunoglobulins, whereas those with IIMs-ILD with mycophenolate mofetil, azathioprine, cyclophosphamide, or rituximab.

At multivariable analysis, high scores of MMT-8, anti-Jo1, anti-MDA5 and anti-Ro52, RP and mechanic's hands were independently associated with ILD. However, heliotrope rash was negatively associated with the occurrence of ILD (table 2).

Subgroup analysis evaluating radiological patterns and their association with clinical and functional variables

HRCT scan at IIMs-ILD diagnosis was available for fully radiological assessment in 78 out of 125 patients (62%). Patients with IIMs-ILD without complete HRCT images

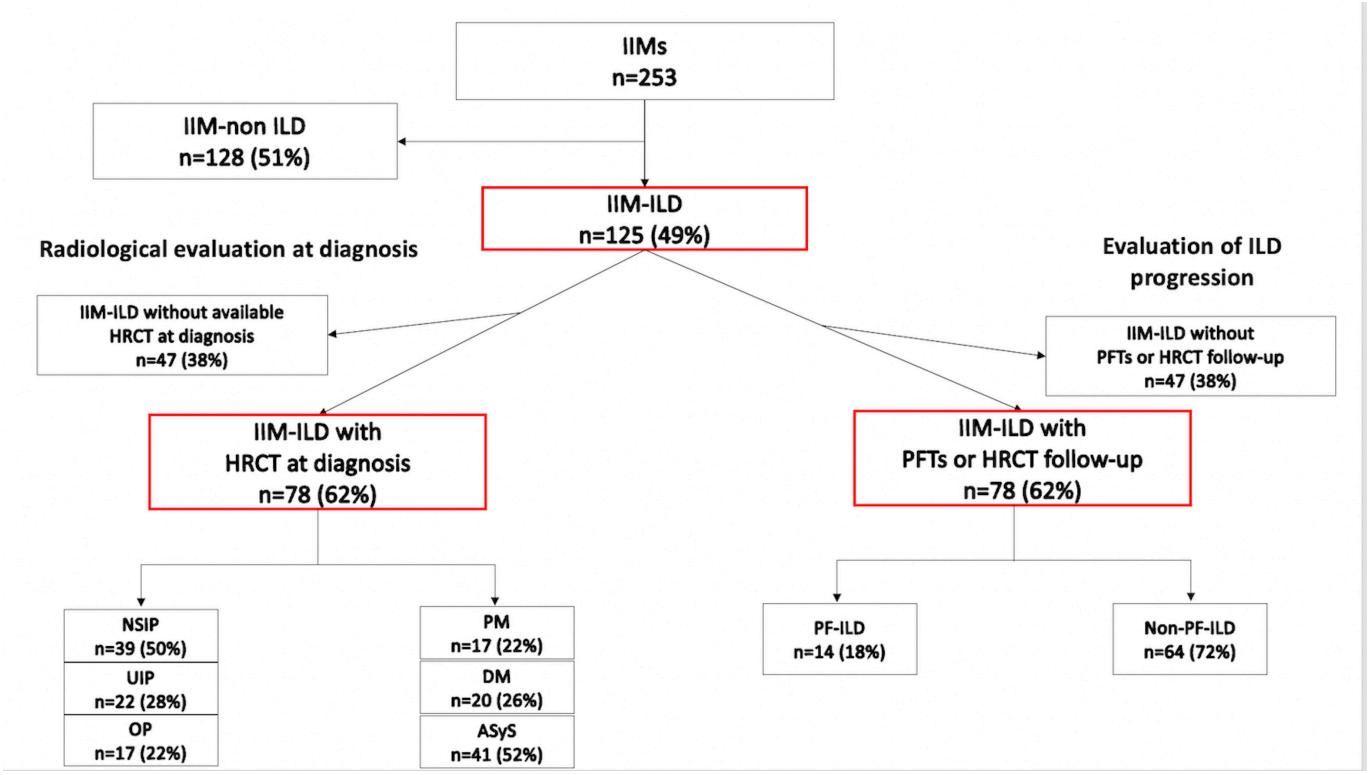

Figure 1 IIM cohort. The IIM cohort has been characterised in two groups according to the presence (IIM-ILD) or absence (IIM-non ILD) of interstitial lung involvement on chest CT scan. Moreover, the IIM-ILD population has been categorised according to the radiological pattern detectable on CT scan at diagnosis and according to the progressive fibrosing criteria.[17] ASyS, anti-synthetase syndrome; DM, dermatomyositis; HRCT, high resolution CT; ILD, interstitial lung disease; IIMs, idiopathic inflammatory myopathies; NSIP, non-specific pneumonia; OP, organising pneumonia; PF, progressive fibrosing; PFTs, pulmonary function tests; PM, polymyositis; UIP, usual interstitial pneumonia.

for review and those with available HRCT showed no substantial differences in terms of clinical and serological variables, except for a longer follow-up in the former group (*data not shown*). We performed a subgroup analysis according to the predominant radiological pattern: NSIP (n=39, 50%), UIP (n=22, 28%) and OP (n=17, 22%). Demographic, clinical, serological and functional data in the three subgroups at IIM-ILD diagnosis are summarised in online supplemental table 2. Notably, lung involvement was always detected before the diagnosis of IIM in the OP group versus NSIP group (p=0.01), and UIP group (p=0.04). Moreover, the OP group displayed significantly higher levels of baseline CK compared with UIP (p=0.01), but not NSIP (p=ns), and a lower MMT-8 score compared with both NSIP (p=0.008) and UIP (p=0.003).

When IIM-ILD population was subgrouped based on the three more frequent IIM clinical phenotypes (PM, DM and ASyS) no differences were found in clinical and radiological presentation among groups (online supplemental table 3).

Assessment of ILD progression

A functional and/or radiological 1-year follow-up was available in 78/125 patients (62%).

According to the 2022 guidelines definition,[18] 14/78 (18%) patients were subgrouped into PF-ILD and 64/78 (82%) patients in not PF-ILD. An example of radiological progression on the CT scan of one patient with IIM-ILD enrolled in our study is reported in online supplemental figure 2.

Demographic, clinical, serological and functional data are summarised in table 3. The two subgroups did not differ with regard to age, sex and IIM clinical phenotype and three patients (4%) died during the follow-up. The PF-ILDs presented a higher prevalence of positive anti-MDA5 antibodies compared with non-PF-ILDs (29% vs 6%, p=0.03), with no other significant differences in the autoantibody profile. The PF-ILDs presented a higher prevalence of xerophthalmia (29% vs 5%, p=0.02) and xerostomia (36% vs 6%, p=0.007) at ILD diagnosis compared with non-PF-ILDs, as well as a higher prevalence of heliotrope rash (29% vs 5%, p=0.02). Regarding pharmacological treatment, the two groups did not differ during the first year after ILD diagnosis (online supplemental table 4). Glucocorticoids were taken by a high percentage of patients in both groups (93 vs 86%, p=0.49) with similar initial dosage, that is, 25 mg/day of prednisone (or equivalent). Mycophenolate mofetil was the immunosuppressant more frequently used in both groups (36% vs. 32%, p=0.81).

Table 1 Clinical and serological features at IIM diagnosis of the overall IIMs population categorised as not associated ILD (IIMs not-ILD) and IIMs-associated ILD (IIMs-ILD)

	Overall population (n=253)	IIMs non-ILD (n=128)	IIMs-ILD (n=125)	P value
Demographics				
Female—n (%)	183 (72)	94 (73)	89 (71)	0.69
Age at diagnosis—years	55 (46–66)	54 (41–67)	57 (49–66)	0.056
History of cancer—n (%)	37 (15)	20 (16)	17 (14)	0.64
Follow-up duration—years	6 (3–10)	6 (3–10)	5 (3–9)	0.44
IIM clinical phenotype				
Polymyositis—n (%)	67 (27)	41 (32)	26 (21)	0.047
Dermatomyositis—n (%)	96 (38)	67 (52)	29 (23)	<0.0001
Inclusion body myositis—n (%)	5 (2)	5 (4)	0 (0)	0.06
Necrotising autoimmune myopathy—n (%)	8 (3)	8 (6)	0 (0)	0.007
Anti-synthetase Syndrome—n (%)	77 (30)	7 (5)	70 (56)	<0.0001
Clinical features				
Arthralgia—n (%)	128 (51)	53 (41)	75 (60)	0.003
Arthritis—n (%)	53 (21)	15 (12)	38 (30)	0.0003
Muscular weakness—n (%)	171 (68)	99 (77)	72 (58)	0.001
Fever—n (%)	48 (19)	15 (12)	33 (26)	0.004
Fatigue—n (%)	119 (47)	60 (47)	59 (47)	0.99
Heliotropic rash—n (%)	74 (29)	56 (44)	18 (14)	<0.0001
Gottron's papules—n (%)	40 (16)	23 (18)	17 (14)	0.39
Gottron's sign—n (%)	37 (15)	24 (19)	13 (10)	0.08
Mechanic's hands—n (%)	30 (12)	4 (3)	26 (21)	<0.0001
Raynaud's phenomenon—n (%)	47 (19)	16 (13)	31 (25)	0.02
Dysphonia—n (%)	9 (4)	3 (2)	6 (5)	0.33
Dysphagia—n (%)	58 (23)	42 (33)	16 (13)	0.0002
Xerostomia—n (%)	23 (9)	9 (7)	14 (11)	0.28
Xerophthalmia—n (%)	21 (8)	8 (6)	13 (10)	0.26
Dyspnoea—n (%)	68 (27)	8 (6)	60 (48)	<0.0001
Cough—n (%)	26 (10)	2 (1)	24 (19)	<0.0001
Muscle involvement				
MMT-8 at diagnosis	140 (120–150)	133.5 (112–148)	148 (130–150)	<0.0001
CK at diagnosis—U/L	674 (128–3268)	1264 (173–4960)	433 (100–2255)	0.001
Muscle biopsy—n (%)	108 (43)	70 (55)	38 (30)	<0.0001
Muscle biopsy abnormalities—n (%)	95 (38)	62 (48)	33 (26)	<0.0001
MRI—n (%)	109 (43)	65 (51)	44 (35)	0.01
MRI abnormalities—n (%)	96 (40)	63 (49)	33 (26)	0.0002
Autoantibody profile				
Antinuclear antibodies—n (%)	162 (64)	74 (58)	88 (70)	0.049
Myositis-specific antibodies—n (%)	138 (55)	51 (40)	87 (70)	<0.0001
Myositis-associated antibodies—n (%)	120 (47)	47 (37)	73 (58)	0.0003
Anti-synthetase—n (%)	87 (34)	12 (9)	75 (60)	<0.0001
Anti-Jo-1—n (%)	63 (25)	7 (5)	56 (45)	<0.0001
Anti-PL12—n (%)	13 (5)	4 (3)	9 (7)	0.14
Anti-PL7—n (%)	14 (6)	6 (5)	8 (6)	0.55

Continued

Table 1 Continued

	Overall population (n=253)	IIMs non-ILD (n=128)	IIMs-ILD (n=125)	P value
Anti-PM/Scl—n (%)	29 (11)	12 (9)	17 (14)	0.29
Anti-SSA/Ro—n (%)	80 (32)	23 (18)	57 (46)	<0.0001
Anti-SSB/La—n (%)	10 (4)	6 (5)	4 (3)	0.54
Anti-U1RNP—n (%)	9 (3)	6 (5)	3 (2)	0.33
Anti-Mi2—n (%)	21 (8)	17 (13)	4 (3)	0.005
Anti-Ku—n (%)	9 (3)	4 (3)	5 (4)	0.71
Anti-TIF1γ—n (%)	7 (3)	6 (5)	1 (1)	0.12
Anti-Ro52—n (%)	44 (17)	11 (8)	33 (26)	0.0002
Anti-MDA5—n (%)	10 (4)	1 (1)	9 (7)	0.01
Anti-EJ—n (%)	4 (1.5)	1 (1)	3 (2)	0.37
Anti-SRP—n (%)	16 (6)	12 (9)	4 (3)	0.07
Anti-SAE1—n (%)	3 (1)	3 (2)	0	0.25
Treatment				
Glucocorticoids—n (%)	236 (93)	119 (93)	117 (94)	0.84
Dose at treatment initiation—mg	25 (0–500)	37.5 (5–500)	25 (0–75)	0.01
Methotrexate—n (%)	155 (61)	104 (81)	51 (41)	<0.0001
Mycophenolate mofetil—n (%)	78 (31)	15 (12)	63 (50)	<0.0001
Azathioprine—n (%)	41 (16)	11 (9)	30 (24)	0.0009
Cyclophosphamide—n (%)	17 (7)	2 (1)	15 (12)	0.0008
Rituximab—n (%)	56 (22)	17 (13)	39 (31)	0.0007
Intravenous immunoglobulin—n (%)	61 (24)	39 (30)	22 (18)	0.02

Values are expressed as numbers and (%) or median and ranges, as appropriate.
CK, creatine kinase; IIMs, idiopathic inflammatory myopathies; ILD, interstitial lung disease; MDA5, anti-melanoma differentiation-associated gene; MMT, manual muscle test; SAE, small ubiquitin-like modifier-1 activating enzyme; SRP, signal recognition particle; TIF1γ, transcription intermediary factor 1-gamma.

Univariate and multivariate evaluation of ILD progression risk

At univariate analysis, anti-MDA5 (OR: 6.10; 95% CI 1.30 to 28.4, p=0.02), heliotrope rash (8.00; 95% CI 1.55 to 41.23, p=0.01), xerostomia, xerophthalmia at ILD diagnosis (8.19; 95% CI 1.84 to 36.36, p=0.006; and 8.00; 95% CI 1.55 to 41.2, p=0.01, respectively), were predictive of progression (table 4). However, none of the significant features at the univariate analysis were confirmed as independent predictors of PF-ILD at multivariate analysis.

DISCUSSION

In our large cohort of patients with IIMs-ILD, we found that about 20% developed PF-ILD within 1 year, according to the 2022 guidelines definition. Moreover, we detected some key clinical and serological features strongly associated with ILD diagnosis and HRCT pattern in IIMs, highlighting that fibrotic changes may occur early in IIMs-ILD course.

Among patients with IIMs, we found that those with amyopathic or hypomyopathic features carry a particularly high risk of developing ILD, highlighting that muscular inflammation and pulmonary involvement often have an independent course in IIMs, and supporting a systematic ILD screening in patients with non-severe muscular impairment. The presence of anti-Ro52 antibodies was independently associated with ILD in our multivariate analysis, thus confirming its strong association with lung fibrosis, independently of concomitant anti-synthetase antibodies positivity.[19] Although MSAs and MMAs autoantibodies are useful in identifying IIMs subsets,[20 21] their detection is limited to referral centres. Our patients with mechanic's hands had an estimated 9-fold increased risk of developing ILD versus those without, an association that was recently reported in Asian patients.[22 23] Although mechanic's hands and RP are hallmarks of the anti-synthetase syndrome,[18] these are manifestations that do not occur in all patients with ASyS and may be observed in other IIMs phenotypes. Mechanic's hands are easily detectable and may prompt a thorough ILD screening, hence the importance of clinical features in ILD risk stratification of patients with IIMs.[24] Over 80% of our patients with IIMs-ILD showed signs of ILD at IIMs diagnosis, or developed ILD during the first 5 years of follow-up. Overall, our findings suggest that patients with

Table 2 Demographic and clinical/serological features at IIM diagnosis associated with the occurrence of ILD in the overall IIMs population

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Demographics				
Sex—(male vs female)	1.14 (0.66 to 1.98)	0.62	–	–
Age at diagnosis (years, ≥55 vs <55)	1.71 (1.04 to 2.80)	0.03	1.62 (0.73 to 3.57)	0.22
Clinical features				
Muscular weakness (yes vs no)	0.37 (0.21 to 0.66)	0.001	0.68 (0.28 to 1.63)	0.39
Heliotrope rash (yes vs no)	0.20 (0.11 to 0.37)	<0.0001	0.25 (0.08 to 0.77)	0.01
Dysphagia (yes vs no)	0.28 (0.15 to 0.54)	<0.0001	0.51 (0.19 to 1.37)	0.18
Mechanic's hands (yes vs no)	7.67 (2.58 to 22.7)	<0.0001	8.56 (1.95 to 37.6)	0.004
Raynaud's phenomenon (yes vs no)	2.32 (1.18 to 4.57)	0.01	3.17 (1.22 to 7.66)	0.02
Arthritis (yes vs no)	3.33 (1.69 to 6.53)	<0.0001	0.97 (0.30 to 3.07)	0.96
Muscle involvement				
MMT-8	1.02 (1.01 to 1.04)	<0.0001	1.02 (1.00 to 1.04)	0.03
CK at diagnosis—U/L	1.0 (1.0 to 1.0)	0.36	–	–
Autoantibody profile				
Antinuclear antibodies (yes vs no)	1.62 (0.95 to 2.75)	0.07	1.55 (0.68 to 3.51)	0.29
Anti-Jo-1 (yes vs no)	13.1 (5.64 to 30.2)	<0.0001	4.48 (1.09 to 19.1)	0.04
Anti-Ro52 (yes vs no)	5.64 (2.74 to 11.60)	<0.0001	3.90 (1.42 to 10.7)	0.008
Anti-MDA5 (yes vs no)	9.30 (1.16 to 74.6)	0.03	10.9 (1.09 to 107.8)	0.04
Anti-Mi 2 (yes vs no)	0.20 (0.06 to 0.62)	0.005	0.34 (0.06 to 1.98)	0.23

Values are expressed as OR (95% CI). Logistic regression analysis was used to determine the relationship between clinical/serological data and the occurrence of lung involvement.
CK, creatine phosphokinase; MDA5, anti-melanoma differentiation-associated gene; MMT, manual muscle test.

IIM at risk for ILD should be carefully screened via PFTs and HRCT at baseline, and yearly at least for the first 5 years from IIMs diagnosis.

Half of our IIMs-ILD cohort had an NSIP pattern on HRCT. Patients with OP require particular attention due to their association with higher CK and lower MMT-8 score versus other subgroups, often a precursor of IIM diagnosis. The association between consolidation in the lung and active muscular disease suggest a more inflammatory phenotype of IIM, which may require higher doses of glucocorticoids. In addition, the detection of lung consolidation on HRCT should prompt myositis antibodies testing, even in the absence of concomitant signs/symptoms indicative of IIMs. It also bears noting that over 20% of our patients had a UIP pattern at diagnosis, supporting the emerging concept that fibrosis may be an early event in CTD-ILD.

Almost 20% of our IIM-ILD population developed PF-ILD. In the literature, very little data is available on the risk of developing PF-ILD in patients with CTDs other than SSc. Takei *et al*[11] reported that 27% of patients with CTD in their cohort developed a progressive form of ILD within 24 months, without accounting for each CTD subtype. The Canadian ILD Registry[25] recently published specific data on patients with IIMs-ILD (without describing any features of the IIMs population) showing that over 40% developed PF-ILD, according to the INBUILD criteria which evaluate the occurrence of PF-ILD within 24 months. On the other hand, the 2022 ATS criteria consider a tighter 1-year time frame and are more accurate in the definition of radiographic progression on HRCT. Even in our study, PF-ILD occurred at 1 year in a considerable percentage of patients, suggesting that patients with IIMs-ILD should be more carefully evaluated for ILD progression, not unlike patients with SSc and rheumatoid arthritis. Given the EMA approval of the antifibrotic nintedanib for the treatment of PF-ILD (July 2020), there is a need to refine PF-ILD estimates in specific real-world CTD subgroups.[9] Although IIMs-ILD features are generally thought to be less fibrotic than SSc-ILD, our findings highlighted a considerable proportion of patients with early fibrotic changes; in this regard, two small retrospective studies evaluating the use of nintedanib and pirfenidone in IIMs-ILD provided some positive signs of effectiveness, in addition to the results from the INBUILD trial.[26 27]

We found no differences in clinical and serological characteristics of progressors versus non-progressors. Unlike previously reported data on SSc-ILD,[28 29] male patients with IIMs and those with lower FVC and DLCO

Table 3 Demographic, clinical, serological and functional characteristics at IIM-ILD diagnosis in the IIM-ILD population, categorised as PF-ILD or non-PF-ILD patients

	Total population n=79	PF-ILD n=14	non-PF-ILD n=64	P value
Demographics				
Male—n (%)	24 (30)	5 (36)	19 (29)	0.75
Female—n (%)	55 (70)	9 (64)	46 (72)	
Age at diagnosis—years	57 (18–83)	57.5 (44–81)	57 (18–83)	0.82
Age at ILD diagnosis—years	58 (18–80)	57 (44–80)	58 (18–79)	0.99
Follow-up duration—years	4 (0–22)	2 (0.25–13)	5 (0–22)	0.047
Deaths—n (%)	3 (4)	1 (7)	2 (3)	0.45
IIM clinical phenotype				
Polymyositis—n (%)	16 (20)	3 (21)	13 (20)	0.95
Dermatomyositis—n (%)	15 (19)	3 (21)	12 (19)	
Anti-synthetase syndrome—n (%)	48 (61)	8 (57)	40 (61)	
Clinical features				
Muscular weakness—n (%)	35 (44)	6 (43)	29 (45)	0.90
Dyspnoea—n (%)	46 (58)	8 (47)	38 (54)	0.93
Dysphagia—n (%)	6 (8)	2 (14)	4 (6)	0.28
Fever—n (%)	20 (25)	3 (21)	17 (26)	0.71
Arthritis—n (%)	19 (24)	5 (36)	14 (22)	0.31
Mechanic hands—n (%)	18 (23)	4 (29)	14 (22)	0.73
Heliotropic rash—n (%)	7 (9)	4 (29)	3 (5)	0.02
Raynaud's phenomenon—n (%)	18 (23)	2 (14)	16 (25)	0.63
Gottron's sign—n (%)	6 (8)	1 (7)	5 (8)	0.94
Gottron's papules—n (%)	8 (10)	2 (14)	6 (9)	0.63
Xerophthalmia—n (%)	7 (9)	4 (29)	3 (5)	0.02
Xerostomia—n (%)	9 (11)	5 (36)	4 (6)	0.007
Muscle involvement				
MMT-8 at diagnosis	150 (70–150)	150 (70–150)	150 (70–150)	0.88
CK at diagnosis—U/L	179 (31–7000)	128 (40–4500)	400 (31–7000)	0.30
Myositis (biopsy and/or MRI)—n (%)	34 (43)	3 (21)	31 (48)	0.08
Autoantibody profile				
Myositis-specific antibodies—n (%)	59 (75)	11 (79)	48 (74)	0.38
Myositis-associated antibodies—n (%)	44 (56)	5 (36)	39 (60)	0.14
Anti-synthetase—n (%)	51 (65)	8 (57)	43 (66)	0.55
ENA—n (%)	60 (76)	11 (79)	49 (75)	0.99
ANA—n (%)	56 (71)	8 (57)	48 (74)	0.33
Anti-Jo1—n (%)	36 (46)	5 (36)	31 (48)	0.56
Anti-PL12—n (%)	7 (9)	2 (14)	5 (8)	0.60
Anti-PL7—n (%)	7 (9)	1 (7)	6 (9)	0.99
Anti-Pm/Scl—n (%)	13 (16)	0 (0)	13 (20)	0.11
Anti-SSA—n (%)	37 (47)	6 (43)	31 (48)	0.78
Anti-SSB—n (%)	4 (5)	0 (0)	4 (6)	1.00
Anti-U1RNP—n (%)	3 (4)	1 (7)	2 (3)	0.45
Anti-Ku—n (%)	3 (4)	1 (7)	2 (3)	0.45
Anti-TIF1γ—n (%)	0 (0)	0 (0)	0 (0)	–
Anti-Ro52—n (%)	28 (35)	4 (29)	24 (37)	0.76

Continued

Table 3 Continued

	Total population n=79	PF-ILD n=14	non-PF-ILD n=64	P value
Anti-MDA5—n (%)	8 (10)	4 (29)	4 (6)	0.03
Anti-EJ—n (%)	1 (1)	0 (0)	1 (2)	0.99
Anti-SRP—n (%)	4 (5)	1 (7)	3 (5)	0.55
Anti-ASMA—n (%)	0 (0)	0 (0)	0 (0)	–
Anti-MI2—n (%)	3 (4)	0 (0)	3 (5)	1.00
Anti-SAE1—n (%)	0 (0)	0 (0)	0 (0)	–
Pulmonary function tests				
FVC—L	2.58 (1.21–4.22)	3.27 (1.56–4.08)	2.57 (1.21–4.22)	0.29
FVC—% pred.	84 (47–146)	89 (53–146)	83 (47–121)	0.36
TLC—L	4.43 (2.22–7.30)	4.27 (3.06–5.39)	4.54 (2.22–7.30)	0.78
TLC—% pred.	80 (47–126)	79 (62–126)	80 (47–119)	0.94
DLCO—% pred.	58 (28–102)	59 (35–91)	55 (21–102)	0.68
KCO—% pred.	78 (42–143)	83 (66–99)	77 (42–143)	0.51

Values are expressed as numbers and (%) or median and Q1–Q3 as appropriate.
ANA, anti-nuclear antibodies; CK, creatine kinase; DLCO, diffusion lung CO; DM, dermatomyositis; ENA, extractable nuclear antigen; FVC, forced vital capacity; IIM, idiopathic inflammatory myopathy; ILD, interstitial lung disease; KCO, carbon monoxide transfer coefficient; MDA5, anti-melanoma differentiation-associated gene; MMT, manual muscle test; PF, pulmonary function; RNP, ribonucleoprotein; SAE, small ubiquitin-like modifier-1 activating enzyme; SRP, signal recognition particle; TIF1γ, transcription intermediary factor 1-gamma; TLC, total lung capacity.

values at diagnosis did not appear to have an increased risk of progression. Similarly, there was no difference between progressors versus non-progressors in HRCT pattern, indicating that the PF-ILD phenotype may occur not only in patients with fibrotic UIP-like pattern but also in those with ground glass and consolidation. Although anti-MDA5 antibodies, heliotrope rash, xerostomia and xerophthalmia were associated with PF-ILD at univariate analysis, none were confirmed as independent predictors. Given the conflicting reports on the prognostic value of positive anti-Ro52 in CTD-ILD,[30 31] it should be noted that this autoantibody specificity was not associated with PF-ILD in our cohort, as found by Vojinovic *et al*.[30] Taken together our data suggest monitoring all patients with IIMs-ILD with PFTs, and HRCT reassessment at 1 year, independently of radiographic phenotype or clinical/serological IIMs characteristics.

The main strength of our study lies in the large number of patients included, given that IIMs are recognised as rare diseases. To the best of our knowledge this is one of the first large multicentre observational studies specifically evaluating the PF-ILD occurrence in patients affected with IIMs, in a well-characterised IIMs cohort with a long-standing follow-up. As limitations, although centres involved in the project are third-level referral centres for CTDs, we cannot rule out slight differences in patient management and follow-up. Second, due to the retrospective design of the study, a limited percentage of incomplete data was tolerated, and we cannot rule out that the lack of a systematic evaluation of respiratory muscle involvement may have partially affected the evaluation of PF-ILD occurrence. Finally, the small sample size of patients with PF-ILD may have limited the identification of independent predictors; in this regard it should be noted that about 50% of our patients with positive MDA5 developed PF-ILD, suggesting that these patients warrant particular attention, nonetheless.

CONCLUSIONS

We found that almost 20% of patients with IIMs-ILD in our cohort developed a PF-ILD phenotype, and we were unable to identify independent predictors. Therefore, it seems reasonable that all patients with IIMs-ILD should be screened via PFTs and repeat HRCT to monitor ILD progression. In addition, we confirmed the close association between specific autoantibodies and some clinical manifestations, and ILD in IIMs. Whereas glucocorticoids and immunosuppressants are the cornerstone of management of IIMs-ILD, the optimal treatment for patients with PF-ILD IIMs is yet to be determined. Further studies are needed to ascertain whether these patients would substantially benefit from antifibrotic treatment as it pertains to morbidity, mortality, and quality of life.

Author affiliations
[1]Rheumatology Unit, Department of Medicine-DIMED, Padova University Hospital, Padova, Italy
[2]Respiratory Disease Unit, Department of Cardiac, Thoracic, Vascular Sciences and Public Health, Padova University Hospital, Padova, Italy
[3]Unit of Advanced Clinical and Translational Imaging, Department of Medicine – DIMED, Padova University Hospital, Padova, Italy
[4]Division of Rheumatology, Department of Medicine (DAME), Academic Hospital "Santa Maria della Misericordia", ASUFC, University of Udine, Udine, Italy

Table 4 Predictive factors of 1-year ILD progression in IIM-ILD population

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Demographics				
Sex—(male vs female)	1.34 (0.39 to 4.54)	0.63	–	–
Age at diagnosis ILD (years, ≥58 vs <58)	0.50 (0.15 to 1.67)	0.26	–	–
Time from diagnosis to ILD—years	0.87 (0.65 to 1.17)	0.38	–	–
Clinical features				
Mechanic's hands (yes vs no)	1.09 (0.26 to 4.48)	0.90	–	–
Heliotropic rash (yes vs no)	8.00 (1.55 to 41.23)	0.01	0.87 (0.13 to 5.65)	0.88
Xerostomia (yes vs no)	8.19 (1.84 to 36.36)	0.006	2.61 (0.23 to 28.6)	0.43
Xerophthalmia (yes vs no)	8.00 (1.55 to 41.2)	0.01	1.17 (0.08 to 16.1)	0.90
Muscle involvement				
MMT-8	0.99 (0.96 to 1.02)	0.75	–	–
CK	1.00 (0.99 to 1.00)	0.40	–	–
Autoantibody profile				
Anti—MDA5 (yes vs no)	6.10 (1.30 to 28.4)	0.02	4.00 (0.53 to 29.8)	0.17
Radiological pattern				
NSIP (yes vs no)	0.72 (0.19 to 2.73)	0.63	–	–
UIP (yes vs no)	2.50 (0.68 to 9.08)	0.16	–	–
OP (yes vs no)	0.50 (0.09 to 2.57)	0.40	–	–
Pulmonary function tests				
FVC (% pred.)	1.02 (0.99 to 1.05)	0.18	–	–
FVC (L)	1.95 (0.67 to 5.70)	0.22	–	–
DLCO (% pred.)	1.07 (0.97 to 1.04)	0.70	–	–

Values are expressed as OR (95%CI).
CK, creatine kinase; DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity; IIM, idiopathic inflammatory myopathies; ILD, interstitial lung disease; MDA5, anti-melanoma differentiation-associated gene; MMT-8, manual muscle testing; NSIP, non-specific interstitial pneumonia; OP, organising pneumonia; UIP, usual interstitial pneumonia.

[5]Department of Experimental and Clinical Medicine, University of Firenze, and Interdisciplinary Internal Medicine Unit, Behçet Centre and Lupus Clinic, AOU Careggi Hospital of Florence, Firenze, Italy
[6]Institute of Radiology, Department of Medicine (DAME), Academic Hospital "Santa Maria della Misericordia", ASUFC, University of Udine, Udine, Italy
[7]Centre for Inflammatory Diseases, Monash University Department of Medicine, Monash Medical Centre, Clayton, Victoria, Australia
[8]Department of Radiology, Azienda USL Toscana Centro, Mugello Hospital, Borgo San Lorenzo, Italy
[9]Unit of Internal Medicine and Hepatology, Department of Medicine, University-Teaching Hospital of Padova, Padova, Italy
[10]Service de Rhumatologie, Hôpital Cochin, APHP, Université Paris Cité Faculté de Santé, Paris, Île-de-France, France

Contributors EZ and EC contributed equally to this paper as first authors. EB and Lla contributed equally to this paper as senior authors. EZ, EC, EB and Lla—study conception and design. EZ, EC—drafted manuscript. EZ, EC, GC, CG, AF, EDZ, MG, Lle, ET, DM, LC, GE, FG, SB, AM, BM, AG, JA, LQ, YA, AD, PS, EB and Lla—collected clinical data, contributed to analysis and interpretation of the results and critically reviewed the manuscript. All authors approved the submitted manuscript. EZ, EC, EB and Lla are guarantors for this manuscript and attest that all listed authors meet authorship criteria.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests EZ and EB report personal and consulting fees from Boehringer Ingelheim. JA and YA report consulting fees from Boehringer Ingelheim. PS reports institutional grants and personal fees from PPM Services, Boehringer Ingelheim and Roche; consulting fees from Boehringer Ingelheim; non-financial support from PPM Services and Boehringer Ingelheim, and personal fees from Galapagos, Chiesi, Novartis, Lupin, Pieris and Santhera Pharmaceuticals.

Patient consent for publication Not applicable.

Ethics approval The study protocol was in compliance with the ethical guidelines of the 1975 Declaration of Helsinki, and it was approved by the Ethics committee—University Hospital of Padova—number 5505/AO/22. Informed consent was waived due to the retrospective nature of the study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

ORCID iDs
Elisabetta Zanatta http://orcid.org/0000-0002-4845-5413
Gioele Castelli http://orcid.org/0000-0002-5925-4035
Giacomo Emmi http://orcid.org/0000-0001-9575-8321
Luca Quartuccio http://orcid.org/0000-0002-0134-6439
Andrea Doria http://orcid.org/0000-0003-0548-4983

REFERENCES

1 De Zorzi E, Spagnolo P, Cocconcelli E, *et al*. Thoracic involvement in systemic autoimmune rheumatic diseases: pathogenesis and management. *Clin Rev Allergy Immunol* 2022;63:472–89.
2 Zanatta E, Codullo V, Avouac J, *et al*. Systemic sclerosis: recent insight in clinical management. *Joint Bone Spine* 2020;87:293–9.
3 Hoffmann-Vold A-M, Distler O, Murray B, *et al*. Setting the international standard for longitudinal follow-up of patients with systemic sclerosis: a Delphi-based expert consensus on core clinical features. *RMD Open* 2019;5:e000826.
4 Egashira R. High-resolution CT findings of myositis-related interstitial lung disease. *Medicina (Kaunas)* 2021;57:692.
5 Cottin V. Treatment of progressive fibrosing interstitial lung diseases: a milestone in the management of interstitial lung diseases. *Eur Respir Rev* 2019;28:190109.
6 Kolb M, Vašáková M. The natural history of progressive fibrosing interstitial lung diseases. *Respir Res* 2019;20:57.
7 Zanatta E, Huscher D, Ortolan A, *et al*. Phenotype of limited cutaneous systemic sclerosis patients with positive anti-topoisomerase I antibodies: data from the EUSTAR cohort. *Rheumatology (Oxford)* 2022;61:4786–96.
8 Cottin V, Hirani NA, Hotchkin DL, *et al*. Presentation, diagnosis and clinical course of the spectrum of progressive-fibrosing interstitial lung diseases. *Eur Respir Rev* 2018;27:180076.
9 Simpson T, Barratt SL, Beirne P, *et al*. The burden of progressive fibrotic interstitial lung disease across the UK. *Eur Respir J* 2021;58:2100221.
10 Flaherty KR, Wells AU, Cottin V, *et al*. Nintedanib in progressive fibrosing interstitial lung diseases. *N Engl J Med* 2019;381:1718–27.
11 Takei R, Brown KK, Yamano Y, *et al*. Prevalence and prognosis of chronic fibrosing interstitial lung diseases with a progressive phenotype. *Respirology* 2022;27:333–40.
12 Wilfong EM, Aggarwal R. Role of Antifibrotics in the management of idiopathic inflammatory myopathy associated interstitial lung disease. *Ther Adv Musculoskelet Dis* 2021;13:1759720X211060907.
13 Bohan A, Peter JB. Polymyositis and dermatomyositis. *N Engl J Med* 1975;292:344–7.
14 Hoogendijk JE, Amato AA, Lecky BR, *et al*. 119Th ENMC international workshop: trial design in adult idiopathic inflammatory myopathies, with the exception of inclusion body myositis. *Neuromuscul Disord* 2004;14:337–45.
15 Lundberg IE, Tjärnlund A, Bottai M, *et al*. 2017 European League against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. *Ann Rheum Dis* 2017;76:1955–64.
16 Ghirardello A, Doria A. New insights in myositis-specific autoantibodies. *Curr Opin Rheumatol* 2018;30:614–22.
17 Raghu G, Remy-Jardin M, Richeldi L, *et al*. Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults: an official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2022;205:e18–47.
18 Cavagna L, Meloni F, Meyer A, *et al*. Clinical spectrum time course in non-Asian patients positive for anti-MDA5 antibodies. *Clin Exp Rheumatol* 2022;40:274–83.
19 Musset L, Allenbach Y, Benveniste O, *et al*. Anti-HMGCR antibodies as a biomarker for immune-mediated necrotizing myopathies: a history of Statins and experience from a large International multi-center study. *Autoimmun Rev* 2016;15:983–93.
20 Iaccarino L, Ghirardello A, Bettio S, *et al*. The clinical features, diagnosis and classification of dermatomyositis. *J Autoimmun* 2014;48–49:122–7.
21 Xing X, Li A, Li C. Anti-Ro52 antibody is an independent risk factor for interstitial lung disease in dermatomyositis. *Respir Med* 2020;172:106134.
22 Huang H-L, Lin W-C, Lin P-Y, *et al*. The significance of myositis autoantibodies in idiopathic inflammatory myopathy concomitant with interstitial lung disease. *Neurol Sci* 2021;42:2855–64.
23 Gasparotto M, Gatto M, Saccon F, *et al*. Pulmonary involvement in antisynthetase syndrome. *Curr Opin Rheumatol* 2019;31:603–10.
24 Ghirardello A, Borella E, Beggio M, *et al*. Myositis autoantibodies and clinical phenotypes. *Auto Immun Highlights* 2014;5:69–75.
25 Hambly N, Farooqi MM, Dvorkin-Gheva A, *et al*. Prevalence and characteristics of progressive fibrosing interstitial lung disease in a prospective registry. *Eur Respir J* 2022;60:2102571.
26 Li T, Guo L, Chen Z, *et al*. Pirfenidone in patients with rapidly progressive interstitial lung disease associated with clinically amyopathic dermatomyositis. *Sci Rep* 2016;6:33226.
27 Liang J, Cao H, Yang Y, *et al*. Efficacy and tolerability of nintedanib in idiopathic-inflammatory-myopathy-related interstitial lung disease: a pilot study. *Front Med* 2021;8:1–14.
28 Distler O, Assassi S, Cottin V, *et al*. Predictors of progression in systemic sclerosis patients with interstitial lung disease. *Eur Respir J* 2020;55:1902026.
29 Hoffmann-Vold A-M, Allanore Y, Alves M, *et al*. Progressive interstitial lung disease in patients with systemic sclerosis-associated interstitial lung disease in the EUSTAR database. *Ann Rheum Dis* 2021;80:219–27.
30 Vojinovic T, Cavazzana I, Ceruti P, *et al*. Predictive features and clinical presentation of interstitial lung disease in inflammatory myositis. *Clin Rev Allergy Immunol* 2021;60:87–94.
31 Ferreira JP, Almeida I, Marinho A, *et al*. Anti-Ro52 antibodies and interstitial lung disease in connective tissue diseases excluding scleroderma. *ISRN Rheumatol* 2012;2012:415272.