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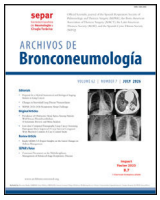

Original Article

Longitudinal Trajectories of Antisynthetase Syndrome-associated Interstitial Lung Disease

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ABSTRACT

Objectives: Interstitial lung disease (ILD) is the principal determinant of morbidity and mortality in antisynthetase syndrome (ASyS). Data regarding ASyS-ILD trajectory phenotypes and factors influencing ILD clinical course remain scarce. We aimed to identify longitudinal ILD trajectories in patients with ASyS-ILD.
Methods: A total of 92 patients with ASyS and ILD diagnosed by high-resolution computed tomography (HRCT), with forced vital capacity (FVC) measurement at ILD diagnosis and at least one additional measurement during follow-up, were included. Latent class mixed models (LCMMs) and linear mixed-effects models were performed to determine groups of patients with similar FVC trajectories and to identify risk factors associated with longitudinal FVC change.
Results: The 3-class model demonstrated the best fit. Class 1 ($n = 17$) had intermediate baseline FVC but declined over time, with higher rates of ILD relapse, pulmonary hypertension, and chronic respiratory failure. Class 2 ($n = 44$) included younger patients with higher baseline FVC that remained stable during follow-up. Class 3 ($n = 31$) had lower baseline FVC and more rapidly progressive ILD at diagnosis but improved over time. In mixed-effects models, nonspecific interstitial pneumonia and organizing pneumonia patterns were associated with a more favorable longitudinal FVC trajectory ($\beta = 6.5$; 95%CI, 1.8–11; $P = .008$ and $\beta = 7.7$; 95%CI, 2.0–13; $P = .009$, respectively).
Conclusions: We identified three phenotypes of ILD trajectories in patients with ASyS, including one group with declining FVC and poor respiratory prognosis. HRCT ILD pattern was the factor most predictive of longitudinal FVC change.

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Abbreviations: ARS, aminoacyl-transfer RNA synthetase; ASyS, antisynthetase syndrome; CK, creatine kinase; CT, computed tomography; DLCO, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; IIM, idiopathic inflammatory myopathy; ILD, interstitial lung disease; IQR, interquartile range; LCMM, latent class mixed model; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; PFT, pulmonary function test; PH, pulmonary hypertension; RP-ILD, rapidly progressive interstitial lung disease; SARD, systemic autoimmune rheumatic disease; UIP, usual interstitial pneumonia.

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Introduction

Antisynthetase syndrome (ASyS) is a subtype of idiopathic inflammatory myopathy (IIM) characterized by anti-aminoacyl-transfer RNA synthetase (anti-ARS) antibodies and heterogeneous clinical signs, including fever, myositis, interstitial lung disease (ILD), mechanic's hands, polyarthralgia or polyarthritis, and Raynaud phenomenon [1]. ILD affects more than 75% of patients and remains the major determinant of morbidity and mortality, sometimes leading to acute or chronic respiratory failure [2,3]. Early identification of patients at high risk of respiratory deterioration is therefore essential to optimize management and tailor treatment of ASyS-ILD.

A major objective in ILD management is assessment of the risk of disease progression over time [4]. In ASyS, ILD may relapse during follow-up even after initial improvement with first-line therapy [5]. In a recent Swedish IIM cohort, anti-Jo-1 antibodies emerged as a risk factor for relapse after glucocorticoid-free remission [6]. Although most studies have assessed ILD severity at diagnosis and long-term pulmonary outcomes in ASyS, longitudinal data regarding ILD course remain scarce. Therefore, ILD trajectory phenotypes and factors influencing longitudinal ILD clinical course require further investigation.

Forced vital capacity (FVC) is a well-established measure of respiratory function for ILD monitoring and commonly serves as the primary endpoint in clinical trials and observational studies of systemic autoimmune rheumatic disease-associated ILD (SARD-ILD) [7,8].

We aimed to identify and characterize distinct subgroups of patients with ASyS-ILD according to longitudinal FVC trajectories, without prior assumptions, and to examine factors associated with significant longitudinal FVC changes in this population.

Methods

Study population

We conducted a multicenter cohort study in seven reference centers within the Myosit'EST network in northeastern France. Patients were recruited from rheumatology, clinical immunology, and pulmonology departments. Inclusion criteria were: (1) age ≥18 years; (2) definite ASyS according to the proposed 2024 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria [9]; (3) positivity for anti-ARS antibodies (anti-Jo-1, PL-7, PL-12, EJ, or OJ); (4) ILD documented by HRCT; and (5) availability of baseline FVC measurement at ILD diagnosis and at least one follow-up FVC measurement. Anti-Jo-1 antibodies were identified by immunoprecipitation or enzyme-linked immunosorbent assay (ELISA), whereas non-anti-Jo-1 antibodies were identified by line/dot immunoblot assays. Patients with substantial missing baseline data or with multiple or rare anti-ARS antibodies were excluded because of uncertain antibody profiles or limited assay reliability. Associated systemic autoimmune rheumatic diseases (SARDs) were defined according to international classification criteria [10–13].

In accordance with French legislation, written informed consent was not required; participants received an information notice and nonopposition form. The study was approved by the local ethics committee and registered at ClinicalTrials.gov (NCT04924465).

ILD outcomes and definitions

FVC was the primary endpoint and was expressed as percentage predicted according to the Global Lung Function Initiative (GLI) equations, enabling longitudinal comparisons [14]. Diffusing capacity of the lung for carbon monoxide (DLCO) was evaluated as a secondary endpoint.

Rapidly progressive ILD (RP-ILD) was defined as acute respiratory failure at diagnosis (PaO_2 <60 mmHg or oxygen requirement) without an alternative cause, or rapid worsening within 3 months, adapted from Wu et al. [15], defined by at least two of the following criteria: (1) increased ILD extent on HRCT, (2) worsening dyspnea, or (3) ≥5% relative decline in predicted FVC. ASyS-ILD relapse was defined as new bilateral ground-glass opacities on HRCT after initial improvement, without alternative causes, requiring intensification of immunosuppressive therapy [16]. Chronic respiratory failure was defined as PaO_2 <70 mmHg at rest on room air on at least two occasions separated by 2 weeks. Pulmonary hypertension (PH) was confirmed by right heart catheterization with mean pulmonary artery pressure (mPAP) ≥20 mmHg [17].

Muscle involvement was defined by creatine kinase (CK) levels ≥2 times the upper limit of normal and/or active inflammatory lesions on magnetic resonance imaging (muscle edema and/or muscle contrast enhancement), myopathic electromyography findings, or biopsy-confirmed myositis. Severe muscle involvement was defined as CK ≥10 times the upper limit of normal, severe proximal muscle weakness (Medical Research Council score ≤3/5), or severe dysphagia [18]. Skin involvement included mechanic's hands or typical dermatomyositis lesions. Microvascular involvement included Raynaud phenomenon, distal ischemic lesions, or abnormal nailfold capillaroscopy findings. Cancer-associated myositis was defined as cancer occurring within 3 years before or after ASyS onset.

Data collection

Data were retrospectively collected from ILD diagnosis to the last follow-up visit at the time of study inclusion. Clinical status, pulmonary function tests (PFTs), HRCT findings, treatments, extrarespiratory manifestations, and ILD outcomes (relapse, PH, chronic respiratory failure, and survival) were recorded longitudinally. ILD pattern and extent were based on radiologist reports when available.

Statistical analyses

Latent class mixed models (LCMMs) were used to identify patient subgroups according to longitudinal FVC and DLCO trajectories. LCMMs assume a finite number of latent classes with distinct average trajectories. The optimal number of classes was selected according to Akaike and Bayesian information criteria, posterior class-membership probabilities (>0.7–0.8), and clinical interpretability [19,20]. Baseline FVC at ILD diagnosis defined time 0. To ensure stable and interpretable trajectory estimation, follow-up was censored after visit 8 because beyond this time point more than 50% of observations were missing. LCMM-defined trajectory classes were subsequently used as exposure groups in survival analyses evaluating chronic respiratory failure using Kaplan–Meier estimates, log-rank tests, and Cox proportional hazards models. Quantitative variables are reported as medians (IQRs), and categorical variables as number (%). Groups were compared using the *t* test or Mann–Whitney *U* test for continuous variables and the chi-square or Fisher's exact test for categorical variables. To assess robustness of trajectory classification, a sensitivity analysis restricted LCMMs to patients with at least three FVC measurements (i.e., baseline plus at least two follow-up assessments).

Linear mixed-effects models with Gaussian errors were used to identify factors associated with ≥5% absolute change in predicted FVC over time in patients with at least three FVC measurements. Covariates were selected a priori according to clinical expertise. Time, candidate predictors, and time-by-covariate inter-

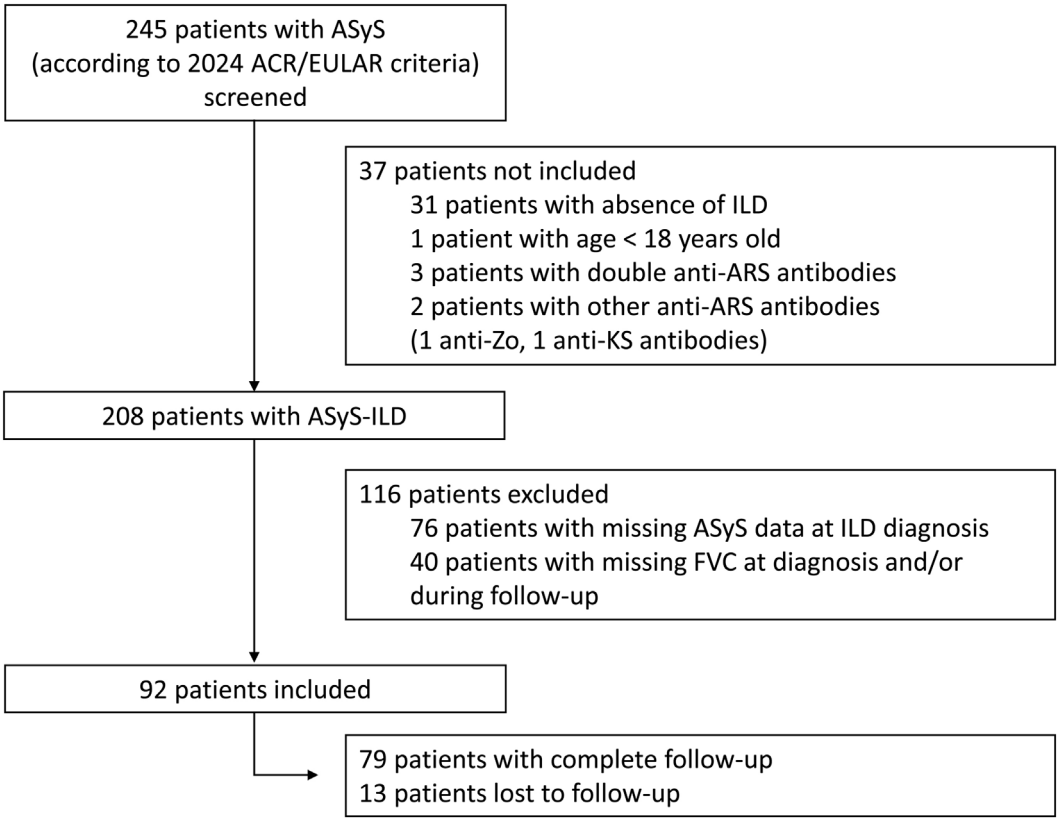

Fig. 1. Flowchart of the study. ACR, American College of Rheumatology; anti-ARS antibodies, anti-aminoacyl-transfer RNA synthetase antibodies; ASyS, antisynthetase syndrome; ASyS-ILD, antisynthetase syndrome-associated interstitial lung disease; EULAR, European Alliance of Associations for Rheumatology; FVC, forced vital capacity; ILD, interstitial lung disease.

actions were first assessed in univariable analyses. Variables with $P < .10$ for either the main effect or interaction term were retained in multivariable models. Main effects represent baseline differences between groups (or per-unit change for continuous covariates), whereas time-by-covariate interactions describe how the rate of FVC change over time varies according to each variable. Random intercepts and, when supported, random slopes with unstructured covariance matrices accounted for within-patient correlation. Competing models were compared using information criteria and residual diagnostics. A Gaussian mixed-effects model provided the best balance between goodness-of-fit and parsimony and was retained for inference (Appendices 1–4). Similar models were used for DLCO trajectories, defining significant change as ≥10% absolute variation over 5 years.

All tests were 2-sided with $\alpha = 0.05$. Analyses were performed using R version 4.3.0.

Results

General characteristics

Among 208 patients with ASyS-ILD screened, 92 were included (Fig. 1). Most participants were women (72%), with a median age at ASyS diagnosis of 54 years (IQR, 46–65 years) (Table S1). Anti-Jo-1, anti-PL-7, anti-PL-12, and anti-EJ antibodies were present in 61%, 15%, 14%, and 10% of patients, respectively; no anti-OJ antibodies were identified.

ILD was present at ASyS diagnosis in 91% of patients. Among the 8 patients diagnosed during follow-up [5], were identified within 3 months after ASyS diagnosis. At ILD diagnosis, median FVC was 72% predicted (IQR, 61%–85%) and median DLCO was 50% predicted (IQR, 42%–63%). The most frequent HRCT pattern was nonspecific interstitial pneumonia (NSIP; 79%), and RP-ILD was present in 33% of patients.

Median follow-up duration was 43 months (IQR, 27–70 months), with 13 patients lost to follow-up (Table S2). During follow-up, 12% developed confirmed PH and 23% progressed to chronic respiratory failure. Patients received a median of three treatments (IQR, 2–4), most commonly glucocorticoids (93%), mycophenolate mofetil (48%), rituximab (41%), and methotrexate (36%).

Compared with the 40 excluded patients with missing serial PFT data, included patients had similar demographic, serological, and extrapulmonary characteristics (Table S3). In contrast, excluded patients had more severe respiratory involvement at ILD diagnosis.

Longitudinal FVC trajectories

Latent class mixed models (LCMMs) with 1–6 classes were compared (Appendix 5), and a 3-class model was selected according to information criteria, class separation, posterior probabilities (74.7%–83.1%; Appendix 6), and clinical interpretability. Class-specific comparison tables are presented in Tables S4–S6.

Class 1 ($n = 17$) demonstrated progressive FVC decline (Fig. 2), with higher rates of ILD relapse, PH (47%), and chronic respiratory failure (53%). Anti-Ro52 antibodies tended to be more common (73%), and patients received a greater number of treatments (Table 1).

Class 2 ($n = 44$) had preserved baseline FVC without clear long-term decline, younger age, and frequent joint involvement (66%) and mechanic's hands (39%). RP-ILD at diagnosis was less common than in Class 3.

Class 3 ($n = 31$) had lower baseline FVC but showed marked improvement over time. RP-ILD at diagnosis was more frequent

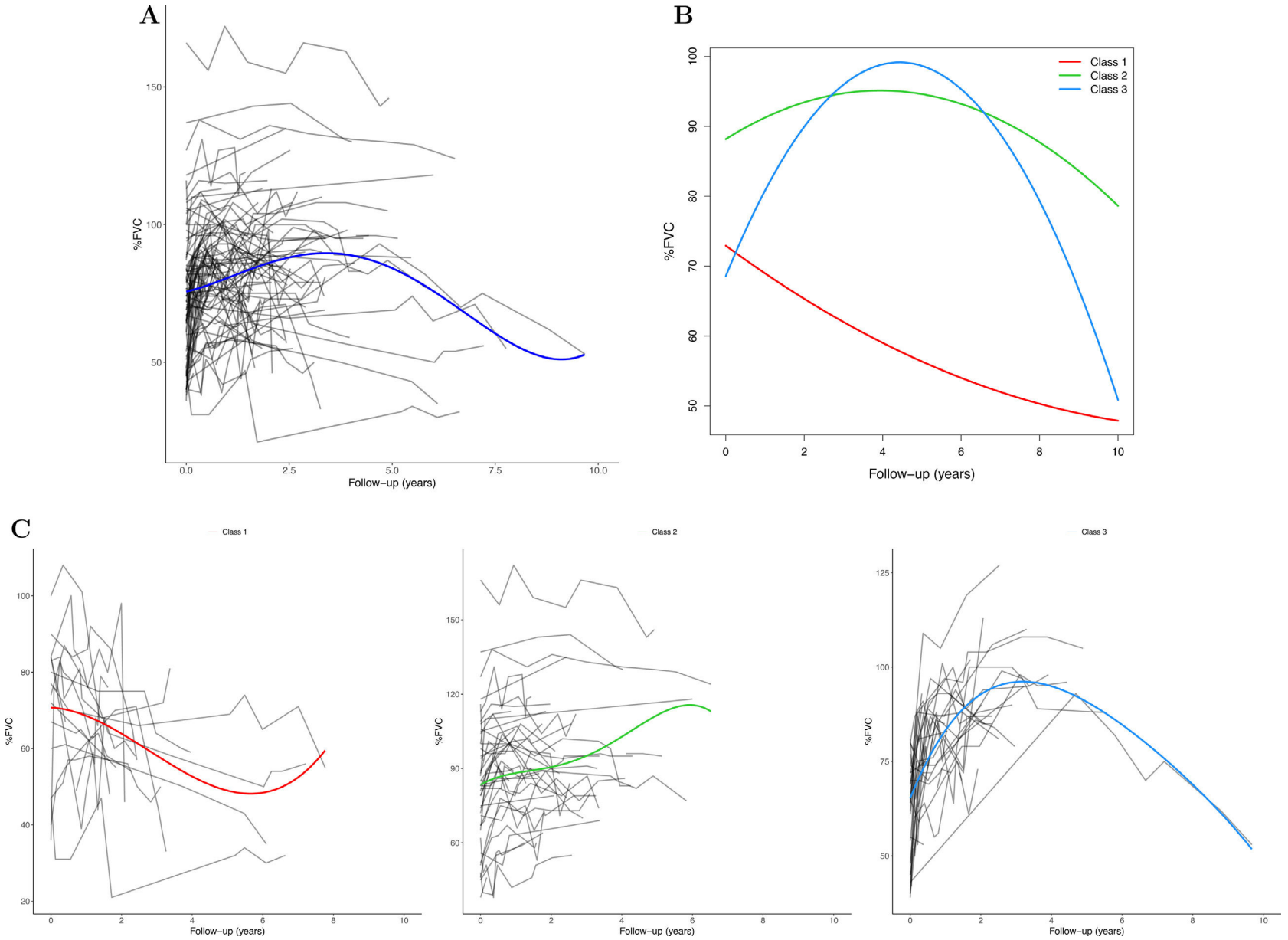

Fig. 2. Three-class latent class mixed model (LCMM) trajectories of FVC over time. (A) Spaghetti plot of all individual trajectories and the average trend estimated using B-splines. (B) FVC trajectories over time according to the 3-class LCMM. The trajectories correspond to LCMM-predicted mean FVC values for each latent class, obtained from the fitted mixture model on a regular time grid. These curves represent model-based class-specific means under the parametric form assumed for the trajectories and therefore appear smoother and may differ slightly from the empirical smoothed curves. (C) Spaghetti plot of the 3-class LCMM with modeled trajectories estimated using B-splines. The trajectories result from spline-based smoothing of observed FVC measurements over time after plotting individual patient curves. These curves reflect the raw longitudinal data, including irregular timing of visits and measurement variability. Time 0 was defined as the date of baseline percentage predicted FVC at ILD diagnosis. %FVC, percentage predicted forced vital capacity; LCMM, latent class mixed model.

Table 1
Comparison of the three classes derived from latent class mixed models for FVC.

Variable	Class 1 (*N* = 17)	Class 2 (*N* = 44)	Class 3 (*N* = 31)
Demographics			
Female sex, *n*/*N* (%)	13/17 (76)	33/44 (75)	20/31 (65)
Age, y[†]	61 (54–68)	**48 (43–59)**c	**58 (54–68)**
Comorbidities			
Cancer-associated myositis, *n*/*N* (%)	4/17 (24)	3/44 (7)	3/31 (10)
Overlapping SARD, *n*/*N* (%)	1/17 (6)	10/44 (23)	5/31 (16)
Clinical signs at ASyS onset			
Skin involvement, n/N (%)			
Mechanic's hands	5/17 (29)	17/44 (39)	8/31 (26)
Typical dermatomyositis signs	2/17 (12)	8/44 (18)	7/31 (23)
Microvascular involvement, *n*/*N* (%)	8/17 (47)	18/44 (41)	10/31 (32)
Joint involvement, *n*/*N* (%)	8/17 (47)	29/44 (66)	18/31 (58)
Muscle involvement, *n*/*N* (%)	10/17 (59)	25/44 (57)	15/31 (48)
Severe muscle involvement, *n*/*N* (%)	6/17 (35)	15/44 (34)	7/31 (23)
Fever, *n*/*N* (%)	5/17 (29)	10/44 (23)	10/31 (32)
Pericarditis and/or myocarditis, *n*/*N* (%)	2/17 (12)	2/44 (5)	2/31 (7)
Antibodies at ASyS diagnosis			
Anti-Jo-1 antibodies, *n*/*N* (%)	11/17 (65)	29/44 (66)	16/31 (52)
Anti-PL-7 antibodies, *n*/*N* (%)	1/17 (6)	8/44 (18)	5/31 (16)
Anti-PL-12 antibodies, *n*/*N* (%)	3/17 (18)	4/44 (9)	6/31 (19)
Anti-EJ antibodies, *n*/*N* (%)	2/17 (12)	3/44 (7)	4/31 (13)
Anti-Ro52 (TRIM21) antibodies, *n*/*N* (%)	8/11 (73)[‡]	11/26 (42)[*]	11/20 (55)[¥]
Laboratory data at ILD diagnosis			
Creatine kinase, IU/L[†]	988 (300–2200)	889 (154–3532)	370 (73–1612)
C-reactive protein, mg/L[†]	19 (10–32)	**18 (7–44)**c	**33 (18–89)**
ILD outcomes at ILD diagnosis			
Pleural effusion, *n*/*N* (%)	2/17 (12)	4/41 (10)[*]	4/29 (14)[¥]
FVC <70% predicted, *n*/*N* (%)	**6/17 (35)**b	**13/44 (30)**c	**21/31 (68)**
FVC, % predicted[†]	**77 (60–84)**b	**83 (66–102)**c	**64 (48–72)**
DLCO, % predicted[†]	**45 (32–58)**a	**57 (48–72)**c	**46 (36–56)**
ILD HRCT pattern, n/N (%)			
UIP	1/9 (11)[‡]	5/30 (17)[*]	2/17 (12)[¥]
NSIP	7/9 (78)[‡]	23/30 (77)[*]	14/17 (82)[¥]
OP	1/9 (11)[‡]	2/30 (7)[*]	5/17 (29)[¥]
RP-ILD at diagnosis, *n*/*N* (%)	5/17 (29)	11/44 (25)	14/31 (45)
ILD outcomes during follow-up			
Lost to follow-up, *n*/*N* (%)	0/17 (0)	6/44 (14)	7/31 (23)
Number of ILD relapses[†]	**2 (1–3)**a,b	**0 (0–1)**	**0 (0–2)**
Suspected or confirmed PH, *n*/*N* (%)	**8/17 (47)**a	**5/44 (11)**	8/31 (26)
Chronic respiratory failure, *n*/*N* (%)	**9/17 (53)**a,b	**7/44 (16)**	**5/31 (16)**
Death, *n*/*N* (%)	3/17 (18)	9/44 (14)	5/31 (16)
Lung transplantation, *n*/*N* (%)	1/17 (6)	0/44 (0)	0/31 (0)
Number of treatments used during follow-up[†]	4 (2–5)	3 (2–4)	3 (2–4)

Alphabetical superscripts indicate statistically significant differences among subgroups using the Wilcoxon rank-sum test and χ^2 or Fisher exact test. Results shown in bold indicate statistically significant findings ($P < .05$). a Indicates significant differences between Class 1 and Class 2. b Indicates significant differences between Class 1 and Class 3. c Indicates significant differences between Class 2 and Class 3. ASyS, antisynthetase syndrome; DLCO, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; LCMM, latent class mixed model; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; PH, pulmonary hypertension; RP-ILD, rapidly progressive interstitial lung disease; SARD, systemic autoimmune rheumatic disease; UIP, usual interstitial pneumonia.

[†] Data are expressed as median (IQR).

[‡] $N \neq 17$ because of missing data.

[¥] $N \neq 31$ because of missing data.

[*] $N \neq 44$ because of missing data.

(45%), and an organizing pneumonia (OP) pattern was more common than in the other classes. No significant differences were observed in extrapulmonary manifestations or anti-ARS antibody profiles across classes.

Five-year chronic respiratory failure-free survival showed a trend toward poorer outcomes in Class 1 (Fig. S1). In Cox proportional hazards models, Classes 2 and 3 tended to have lower risk of chronic respiratory failure compared with Class 1 (reference group).

In the sensitivity analysis restricted to patients with at least three FVC measurements ($N = 79$), the 3-class structure was preserved with similar trajectories (Fig. S2). However, the declining class was no longer observed as a distinct class and appeared to be partially redistributed into the stable group, whereas clinical characteristics remained consistent with the primary analysis (Tables S7 and S8).

Longitudinal DLCO trajectories

DLCO trajectories were also best described by a 3-class model (Appendix 7), with posterior probabilities ranging from 72.4% to 81.0% (Appendix 8).

Among 78 patients, Class 1 ($n = 28$) showed stable DLCO over time and received more immunosuppressive treatments than

Class 3 (Fig. S3 and Table S9). Class 2 ($n = 9$) demonstrated DLCO decline, more frequent associated SARDs, a tendency toward higher anti-Ro52 positivity, and increased rates of ILD relapse, chronic respiratory failure, and suspected or confirmed PH compared with Class 3. Class 3 ($n = 41$) showed DLCO improvement and fewer ILD relapses. Class-specific comparison tables are presented in Tables S10–S12.

Determinants of lung function change

In univariable analyses, age, cancer-associated myositis, anti-ARS antibodies, RP-ILD at diagnosis, HRCT pattern, and number of treatments were associated with longitudinal FVC change over 5 years ($n = 74$, Table 2).

In multivariable models ($n = 25$), no baseline clinical or serological factor was associated with FVC at inclusion. Significant time-dependent effects were observed. NSIP ($\beta = 6.5$; 95%CI, 1.8–11; $P = .008$) and OP patterns ($\beta = 7.7$; 95%CI, 2.0–13; $P = .009$) were associated with a more favorable longitudinal FVC trajectory. RP-ILD at diagnosis showed a borderline interaction ($\beta = 3.0$; 95%CI, −0.06 to 6.0; $P = .055$).

For DLCO, univariable analyses identified RP-ILD at diagnosis, usual interstitial pneumonia (UIP) pattern, antifibrotic therapy, and number of treatments as associated factors ($n = 77$, Table S13). In multivariable models ($n = 47$), DLCO improved over time overall ($\beta = 5.94$; 95%CI, 0.8–11; $P = .025$), whereas UIP pattern was associated with DLCO decline ($\beta = -8.5$; 95%CI, −16 to 0.7; $P = .032$).

Discussion

We conducted a multicenter study of 92 patients with ASyS-associated ILD to evaluate longitudinal FVC trajectories. Using an unsupervised approach, we identified three distinct trajectory groups after ILD diagnosis: a “stable” class (Class 2) with preserved FVC (∼50% of patients), a “worsening” class (Class 1) with progressive FVC decline and poorer respiratory outcomes, and an “improving” class (Class 3) with severe initial ILD but marked FVC recovery over time.

Patients in the “improving” class represented approximately one-third of the cohort and likely reflected inflammatory ILD, as suggested by the higher frequency of OP pattern and elevated C-reactive protein levels. OP is commonly associated with inflammatory ILD and has been reported more frequently in RP-ILD among patients with IIM-associated ILD [21,22]. In contrast, the “worsening” class, comprising fewer than 20% of patients, was characterized by poorer long-term outcomes, including more ILD relapses, chronic respiratory failure, and PH, despite relatively preserved baseline FVC. No baseline demographic, clinical, or serological characteristics identified this “at-risk” group. Greater use of immunosuppressants or antifibrotic agents in this subgroup likely reflected more refractory disease. Longitudinal respiratory data in ASyS-ILD remain limited. A previous cohort of 69 anti-Jo-1-positive patients showed globally stable FVC over time but did not evaluate trajectory heterogeneity [23]. Our LCMM approach highlights this heterogeneity beyond average longitudinal trends.

Trajectory profiles remained highly similar in sensitivity analyses, supporting robustness of the findings despite some patient reallocation across classes. Restricting analyses to patients with at least three PFT measurements likely introduced selection bias toward patients with better survival and underrepresented severe ILD cases, which may explain why the declining trajectory was no longer identified as a distinct class. In addition, LCMMs model trajectories as continuous functions of time and therefore accommodate variable follow-up duration across patients. However, trajectory estimates beyond 4 years should be interpreted cautiously because of limited data density and potential informative missingness at later time points.

FVC remains a common endpoint in SARD-ILD despite important limitations, including influence of chest wall mechanics, respiratory muscle involvement, and emphysema [7,8,24]. In our cohort, respiratory muscle strength measurements were unavailable in most patients. However, muscle involvement was not associated with FVC decline in mixed-effects models, suggesting limited confounding from muscle disease. Secondary analyses identified three DLCO trajectories similar to those observed for FVC. Patients with declining DLCO also had poorer respiratory outcomes, although these findings should be interpreted cautiously because of the small class size and low model entropy. Only 4 of 9 patients in the DLCO-decline class also belonged to the FVC-decline class, suggesting that pulmonary vascular involvement may partly contribute to DLCO decline.

ASyS-associated ILD generally has a more favorable prognosis than other SARD-ILDs [25]. Our findings confirm favorable outcomes in most patients while identifying a subgroup with progressive respiratory decline requiring closer monitoring. Progressive fibrosing disease and treatment exposure may both have contributed to the observed trajectories. However, LCMMs are descriptive models and do not allow causal assessment of treatment effects or adjustment for time-dependent confounding. Although Class 1 exhibited poorer respiratory outcomes, survival without chronic respiratory insufficiency did not significantly differ among classes, likely because of limited statistical power and relatively few events.

A substantial proportion of patients were recruited from rheumatology or clinical immunology departments. Patients within the “stable” trajectory group may therefore represent individuals with more systemic disease and less predominant ILD, potentially introducing referral bias. Further studies using similar methodology in pulmonology-based cohorts and in other geographic populations are needed to assess reproducibility and generalizability.

Exploratory mixed-effects analyses identified HRCT ILD pattern as a major predictor of longitudinal FVC evolution. NSIP and OP patterns were associated with FVC improvement over time, supporting their more favorable prognosis compared with UIP, as previously reported in IIM-ILD [26–28]. Similarly, a cohort of 118 anti-ARS-positive ILD cases demonstrated FVC improvement in two-thirds of patients, particularly in younger individuals and those without UIP [21]. In contrast, neither autoantibody profile nor treatment exposure was associated with longitudinal FVC change. Similar findings were observed for DLCO.

This study has several limitations related to its retrospective design. Missing longitudinal PFT data led to exclusion of several patients. Analysis of excluded patients suggests that the most severe or rapidly progressive forms of ILD were underrepresented. Consequently, generalizability may be limited, particularly for severe cases in whom PFTs were unavailable at diagnosis. Nevertheless, baseline characteristics and antibody profiles were consistent with previous large ASyS cohorts [2,3,29]. Comorbidities potentially affecting PFTs were not evaluated. Although diagnostic delay may be associated with poorer ILD outcomes in ASyS, the date of symptom onset was unavailable for most patients in our cohort, precluding its evaluation [30]. Recent European Respiratory Society/American Thoracic Society guidelines recommend Z scores for interpretation of lung function [31], whereas we used percentage predicted values according to GLI equations, consistent with most SARD-ILD studies and routine clinical practice [4]. Finally, absence of centralized longitudinal HRCT review precluded reliable identification of progressive fibrosing ILD during follow-up [32].

In conclusion, we identified three distinct ILD trajectory phenotypes in ASyS-ILD, highlighting heterogeneity of disease evolution.

Table 2
Risk factors associated with longitudinal FVC change over time.

Predictor variable	Univariable analysis coefficient	95%CI	*P*-value	Multivariable analysis coefficient	95%CI	*P*-value
Time	–	–	–	−5.35	−19.91 to 9.22	.5
Age at ASyS diagnosis*	0.04	−0.31 to 0.40	.8	−0.76	−2.31 to 0.80	.3
Time × Age at ASyS diagnosis*	**−0.05**	**−0.10 to −0.00**	**.04**	−0.08	−0.27 to 0.11	.4
Male sex	−6.86	−17.1 to 3.4	.19	–	–	–
Time × Male sex	0.08	−1.1 to 1.3	.89	–	–	–
BMI at ASyS diagnosis	−0.31	−1.30 to 0.68	.53	–	–	–
Time × BMI at ASyS diagnosis	0.01	−0.12 to 0.15	.84	–	–	–
Overlapping SARD	2.06	−10.4 to 14.5	.74	–	–	–
Time × Overlapping SARD	−0.65	−2.1 to 0.8	.38	–	–	–
Skin involvement at ASyS diagnosis	−4.5	−14.3 to 5.3	.34	–	–	–
Time × Skin involvement at ASyS diagnosis	0.13	−1.09 to 1.35	.8	–	–	–
Microvascular involvement at ASyS diagnosis	2.0	−7.6 to 11.6	.67	–	–	–
Time × Microvascular involvement at ASyS diagnosis	−0.78	−1.94 to 0.38	.19	–	–	–
Joint involvement at ASyS diagnosis	5.7	−4.3 to 15.8	.26	–	–	–
Time × Joint involvement at ASyS diagnosis	−0.11	−1.37 to 1.14	.8	–	–	–
Muscle involvement at ASyS diagnosis	1.9	−7.5 to 11.4	.69	–	–	–
Time × Muscle involvement at ASyS diagnosis	−0.37	−1.52 to 0.78	.5	–	–	–
Pericarditis and/or myocarditis at ASyS diagnosis	10.5	−10.9 to 31.9	.33	–	–	–
Time × Pericarditis and/or myocarditis at ASyS diagnosis	−2.72	−6.15 to 0.71	.12	–	–	–
Fever at ASyS diagnosis	**−10.4**	**−20.2 to −0.6**	**.04**	−2.90	−57.20 to 51.40	.8
Time × Fever at ASyS diagnosis	0.73	−0.49 to 1.95	.24	−2.43	−6.87 to 2.00	.3
Anti-Jo-1 antibodies at ASyS diagnosis	17.3	−0.4 to 34.9	.05	−15.11	−102.62 to 72.40	.7
Time × Anti-Jo-1 antibodies at ASyS diagnosis	**−4.43**	**−6.66 to −2.21**	**<.001**	−2.88	−10.83 to 5.06	.5
Anti-PL-7 antibodies at ASyS diagnosis	19.1	−2.4 to 40.5	.08	5.64	−93.86 to 105.15	>.9
Time × Anti-PL-7 antibodies at ASyS diagnosis	**−4.96**	**−7.65 to −2.27**	**<.001**	−5.77	−15.02 to 3.49	.2
Anti-PL-12 antibodies at ASyS diagnosis	11.6	−8.5 to 31.7	.25	−8.41	−118.56 to 101.75	.9
Time × Anti-PL-12 antibodies at ASyS diagnosis	−2.23	−4.73 to 0.27	.08	−0.94	−10.82 to 8.94	.9
Anti-Ro52 (TRIM21) antibodies at ASyS diagnosis	−7.2	−19.5 to 5.1	.25	−0.83	−38.57 to 36.91	>.9
Time × Anti-Ro52 (TRIM21) antibodies at ASyS diagnosis	−1.30	−2.87 to 0.27	.10	−0.41	−3.93 to 3.11	.8
C-reactive protein at ILD diagnosis†	**−0.1**	**−0.1 to −0.0**	**.04**	−5.09	−26.09 to 15.92	.6
Time × C-reactive protein at ILD diagnosis†	0.00	−0.00 to 0.01	.49	1.27	−0.79 to 3.32	.2
UIP pattern at ILD diagnosis	8.5	−8.2 to 25.1	.31	26.26	−55.25 to 107.77	.5
Time × UIP pattern at ILD diagnosis	**−2.53**	**−4.42 to −0.64**	**.009**	5.74	−2.87 to 14.35	.2
NSIP pattern at ILD diagnosis	−1.6	−15.6 to 12.5	.82	17.90	−30.36 to 66.16	.4
Time × NSIP pattern at ILD diagnosis	**1.97**	**0.30 to 3.64**	**.02**	**6.52**	**1.75 to 11.28**	**.008**
OP pattern at ILD diagnosis	−10.2	−26.0 to 5.7	.2	5.04	−42.41 to 52.49	.8
Time × OP pattern at ILD diagnosis	**3.35**	**1.05 to 5.66**	**.005**	7.70	**1.97 to 13.44**	**.009**
Rapidly progressive ILD at ILD diagnosis	−10.76	−23.0 to 1.11	.08	−8.45	−44.17 to 27.26	.6
Time × Rapidly progressive ILD at ILD diagnosis	**2.04**	**0.63 to 3.44**	**.005**	2.96	−0.06 to 5.98	.055
Pleural effusion at ILD diagnosis	−8.5	−21.2 to 4.3	.19	–	–	–
Time × Pleural effusion at ILD diagnosis	0.67	−1.02 to 2.35	.44	–	–	–
Number of treatments used during follow-up	−1.5	−4.6 to 1.6	.33	−0.95	−11.05 to 9.15	.8
Time × Number of treatments used during follow-up	**−0.44**	**−0.84 to −0.04**	**.03**	0.55	−0.64 to 1.75	.4
Rituximab	−3.3	−12.7 to 6.2	.49	–	–	–
Time × Rituximab	−0.12	−1.27 to 1.04	.8	–	–	–
Antifibrotic drugs	−19.5	−39.7 to 0.7	.06	−15.41	−103.55 to 72.73	.7
Time × Antifibrotic drugs	−0.50	−2.45 to 1.45	.6	−1.21	−7.71 to 5.29	.7

Gaussian linear mixed-effects model adjusting the continuous outcome for clinical and biological covariates. Coefficients (β estimates) represent the absolute change in the outcome associated with each covariate. Results shown in bold indicate statistically significant findings ($P < .05$). 95%CI, 95% confidence interval; ASyS, antisynthetase syndrome; BMI, body mass index; ILD, interstitial lung disease; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; SARD, systemic autoimmune rheumatic disease; UIP, usual interstitial pneumonia.

† After imputation and log transformation.

* Age expressed in years.

These trajectories may provide clinically relevant prognostic stratification and help guide therapeutic decision-making by identifying patients at higher risk of respiratory decline and poorer outcomes who may require closer monitoring. HRCT ILD patterns were associated with longitudinal FVC evolution, whereas anti-ARS antibody profiles were not, emphasizing the potential prognostic value of radiological assessment. However, these findings should be interpreted cautiously because LCMMs remain primarily descriptive and do not provide a directly applicable individual-level predictive tool. In addition, the relatively small sample size limits identification of robust predictors. External validation in independent cohorts is therefore required to confirm reproducibility and clinical utility of these trajectory phenotypes.

Authors' contributions

PD had full access to all study data and takes responsibility for the integrity of the data and accuracy of the data analysis, including and especially any adverse effects. MB contributed substantially to data curation, investigation, and manuscript writing. HC contributed substantially to data analysis and manuscript writing. TM and RJ contributed substantially to study conceptualization and manuscript writing. AM, LB, KD, SD, BB, HD, PB, GB, JC, NMB, AC, and SV contributed substantially to data curation and manuscript writing. PD contributed substantially to study conceptualization, study design, investigation, and manuscript writing.

The sponsor of this study had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Ethics statement

The study was approved by the local ethics committee of CHRU Nancy (approval number 315) and registered at ClinicalTrials.gov (NCT04924465).

Declaration of generative AI and AI-assisted technologies in the writing process

No artificial intelligence was used.

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Conflicts of interest

None declared.

Data availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.1016/j.arbres.2026.05.015.

References

[1] Marco JL, Collins BF. Clinical signs and treatment of antisynthetase syndrome. Best Pract Res Clin Rheumatol 2020;34, http://dx.doi.org/10.1016/j.berh.2020.101503, 101503.
[2] Cavagna L, Trallero-Araguás E, Meloni F, Cavazzana I, Rojas-Serrano J, Feist E, et al. Influence of antisynthetase antibody specificities on antisynthetase syndrome clinical spectrum and time course. J Clin Med 2019;8:2013, http://dx.doi.org/10.3390/jcm8112013.
[3] Aggarwal R, Cassidy E, Fertig N, Koontz DC, Lucas M, Ascherman DP, et al. Patients with non-Jo-1 anti-tRNA synthetase autoantibodies have worse survival than Jo-1-positive patients. Ann Rheum Dis 2014;73:227–32, http://dx.doi.org/10.1136/annrheumdis-2012-201800.
[4] Antoniou KM, Distler O, Gheorghiu AM, Moor CC, Vikse J, Bizymi N, et al. ERS/EULAR clinical practice guidelines for connective tissue disease-associated interstitial lung disease. Eur Respir J 2026;67, http://dx.doi.org/10.1183/13993003.02533-2024, 2402533.
[5] Matsuda S, Kotani T, Oe K, Nishioka D, Akiyama C, Yamamoto M, et al. Risk prediction model for relapse of anti-synthetase syndrome-associated interstitial lung disease in Japanese multicentre MYKO cohort study. Rheumatology (Oxford) 2026;65:keaf469, http://dx.doi.org/10.1093/rheumatology/keaf469.
[6] Tsuji H, Espinosa-Ortega F, Peralta Garcia I, Dastmalchi M, Lundberg IE, Lodin K. Relapse rate after glucocorticoid-free remission in patients with idiopathic inflammatory myopathies and validation of the International Myositis Assessment and Clinical Studies Group criteria for complete clinical response and worsening. Arthritis Rheumatol 2026;78:936–47, http://dx.doi.org/10.1002/art.43429.
[7] Mankikian J, Caille A, Reynaud-Gaubert M, Agier MS, Bermudez J, Bonniaud P, et al. Rituximab and mycophenolate mofetil combination in patients with interstitial lung disease (EVER-ILD): a double-blind, randomized, placebo-controlled trial. Eur Respir J 2023;61, http://dx.doi.org/10.1183/13993003.02071-2022, 2202071.
[8] Maher TM, Tudor VA, Saunders P, Gibbons MA, Fletcher SV, Denton CP, et al. Rituximab versus intravenous cyclophosphamide in patients with connective tissue disease-associated interstitial lung disease in the UK (RECITAL): a double-blind, double-dummy, randomized, controlled, phase 2b trial. Lancet Respir Med 2023;11:45–54, http://dx.doi.org/10.1016/S2213-2600(22)00359-X.
[9] Zanframundo G, Faghihi Kashani S, Yoshida A, Dourado E, Bauer Ventura I, Rivero Gallegos D, et al. The classification criteria for anti-synthetase syndrome (CLASS) project [abstract]. Arthritis Rheumatol 2024;76(Suppl. 9). Available from: https://acrabstracts.org/abstract/the-classification-criteria-for-anti-synthetase-syndrome-class-project/ [accessed 12 Jun 2026].
[10] Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69:1580–8, http://dx.doi.org/10.1136/ard.2010.138461.
[11] Aringer M, Costenbader K, Daikh D, Brinks R, Mosca M, Ramsey-Goldman R, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Ann Rheum Dis 2019;78:1151–9, http://dx.doi.org/10.1136/annrheumdis-2018-214819.
[12] Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM, et al. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren syndrome: a consensus and data-driven methodology involving 3 international patient cohorts. Arthritis Rheumatol 2017;69:35–45, http://dx.doi.org/10.1002/art.39859.
[13] van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2013;72:1747–55, http://dx.doi.org/10.1136/annrheumdis-2013-204424.
[14] Bowerman C, Bhakta NR, Brazzale D, Cooper BR, Cooper J, Gochicoa-Rangel L, et al. A race-neutral approach to the interpretation of lung function measurements. Am J Respir Crit Care Med 2023;207:768–74, http://dx.doi.org/10.1164/rccm.202205-0963OC.
[15] Wu S, Xiao X, Zhang Y, Zhang X, Wang G, Peng Q. Novel endotypes of anti-synthetase syndrome identified independent of anti-aminoacyl transfer RNA synthetase antibody specificity that improve prognostic stratification. Ann Rheum Dis 2024;83:775–86, http://dx.doi.org/10.1136/ard-2023-225284.
[16] Collard HR, Ryerson CJ, Corte TJ, Jenkins G, Kondoh Y, Lederer DJ, et al. Acute exacerbation of idiopathic pulmonary fibrosis: an international working group report. Am J Respir Crit Care Med 2016;194:265–75, http://dx.doi.org/10.1164/rccm.201604-0801CI.
[17] Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, et al. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2023;61:2200879, http://dx.doi.org/10.1183/13993003.00879-2022.
[18] Kleyweg RP, van der Meché FG, Schmitz PI. Interobserver agreement in the assessment of muscle strength and functional abilities in Guillain-Barré syndrome. Muscle Nerve 1991;14:1103–9, http://dx.doi.org/10.1002/mus.880141111.
[19] Schreiber JB. Latent class analysis: an example for reporting results. Res Social Adm Pharm 2017;13:1196–201, http://dx.doi.org/10.1016/j.sapharm.2016.11.011.
[20] van de Schoot R, Sijbrandij M, Winter SD, Depaoli S, Vermunt JK. The GRoLTS checklist: guidelines for reporting on latent trajectory studies. Struct Equ Modeling 2017;24:451–67, http://dx.doi.org/10.1080/10705511.2016.1247646.
[21] González-Pérez MI, Mejía-Hurtado JG, Pérez-Román DI, Buendía-Roldán I, Mejía M, Falfán-Valencia R, et al. Evolution of pulmonary function in a cohort of patients with interstitial lung disease positive for antisynthetase antibodies. J Rheumatol 2020;47:415–23, http://dx.doi.org/10.3899/jrheum.181141.
[22] Li Y, Gao X, Li Y, Jia X, Zhang X, Xu Y, et al. Predictors and mortality of rapidly progressive interstitial lung disease in patients with idiopathic inflammatory myopathy: a series of 474 patients. Front Med (Lausanne) 2020;7:363, http://dx.doi.org/10.3389/fmed.2020.00363.
[23] Trallero-Araguás E, Grau-Junyent JM, Labirua-Iturburu A, García-Hernández FJ, Monteagudo-Jiménez M, Fraile-Rodriguez G, et al. Clinical signs and long-term outcome of anti-Jo-1 antisynthetase syndrome in a large cohort of Spanish patients from the GEAS-IIM group. Semin Arthritis Rheum 2016;46:225–31, http://dx.doi.org/10.1016/j.semarthrit.2016.03.011.
[24] Lammi MR, Baughman RP, Birring SS, Russell AM, Ryu JH, Scholand M, et al. Outcome measures for clinical trials in interstitial lung diseases. Curr Respir Med Rev 2015;11:163, http://dx.doi.org/10.2174/1573398X11666150619183527.
[25] Graham J, Bauer Ventura I, Newton CA, Lee C, Boctor N, et al. Myositis-specific antibodies identify a distinct interstitial pneumonia with autoimmune features phenotype. Eur Respir J 2020;56, http://dx.doi.org/10.1183/13993003.01205-2020, 2001205.
[26] Bai Z, Shen G, Dong L. Analysis of risk factors of interstitial lung disease and mortality rates in Chinese patients with idiopathic inflammatory myopathy. Int J Rheum Dis 2021;24:815–27, http://dx.doi.org/10.1111/1756-185X.14128.
[27] Cobo-Ibáñez T, López-Longo FJ, Joven B, Carreira PE, Muñoz-Fernández S, Maldonado-Romero V, et al. Long-term pulmonary outcomes and mortality in idiopathic inflammatory myopathies associated with interstitial lung disease. Clin Rheumatol 2019;38:803–15, http://dx.doi.org/10.1007/s10067-018-4353-2.

[28] Marie I, Josse S, Hatron PY, Dominique S, Hachulla E, Janvresse A, et al. Interstitial lung disease in anti-Jo-1 patients with antisynthetase syndrome. Arthritis Care Res (Hoboken) 2013;65:800–8, http://dx.doi.org/10.1002/acr.21895.
[29] Lilleker JB, Vencovsky J, Wang G, Wedderburn LR, Diederichsen LP, Schmidt J, et al. The EuroMyositis registry: an international collaborative tool to facilitate myositis research. Ann Rheum Dis 2018;77:30–9, http://dx.doi.org/10.1136/annrheumdis-2017-211868.
[30] Tang HS, Tang IYK, Ho RTC, Young JKY, Lai BTL, Chung JYK, et al. Clinical heterogeneity and prognostic factors of antisynthetase syndrome: a multicenter retrospective cohort study. Rheumatology (Oxford) 2025;64:212–20, http://dx.doi.org/10.1093/rheumatology/kead671.
[31] Stanojevic S, Kaminsky DA, Miller MR, Thompson B, Aliverti A, Barjaktarevic I, et al. ERS/ATS technical standard on interpretive strategies for routine lung function tests. Eur Respir J 2022;60, http://dx.doi.org/10.1183/13993003.01499-2021, 2101499.
[32] Qiang Y, Wang H, Ni Y, Wang J, Liu A, Du J, et al. Longitudinal change of idiopathic inflammatory myopathy-associated interstitial lung disease on high-resolution computed tomography: a prospective cohort study. BMC Pulm Med 2025;25:503, http://dx.doi.org/10.1186/s12890-025-03962-w.