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# Long-term clinical prognosis of anti-aminoacyl-tRNA synthetase antibodies and interstitial lung disease

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## Abstract

**Introduction** Anti-aminoacyl tRNA synthetase (anti-ARS) antibody is the most common myositis-specific antibody subtype. Anti-ARS antibody-positive myositis is often complicated by interstitial lung disease (ILD), but the clinical progression of anti-ARS antibody-positive ILD (ARS-ILD) remains unclear.

**Method** A prospectively collected, single center longitudinal myositis database was used to retrospectively investigate 131 patients with ARS-ILD based on subtypes of anti-ARS antibodies (Jo-1, PL-7, PL-12, EJ, OJ, and KS). We investigated the occurrence and associated risk factors for pulmonary events, including lung transplantation and pulmonary death, as well as overall mortality at both 5 and 10 years.

**Results** This cohort included those with myositis (n = 97), anti-synthetase syndrome without myositis (n = 17), and other connective tissue diseases (n = 17). In a 5-year period, the overall mortality rate and incidence of pulmonary events were both 15%. Across a 10-year timespan, the overall mortality rate increased to 28%, with pulmonary events observed in 24% of cases. A multivariate analysis during the 5-year follow-up, identified poor prognostic factors for overall mortality included dysphagia, dry eyes, usual interstitial pneumonia (UIP) pattern, and the presence of anti-PL-7 antibody. In the 10-year follow-up, dysphagia, diffusing capacity for carbon monoxide (DLCO)%, and anti-PL-7 antibody were associated with increased mortality. Risk factors for pulmonary events at 5 years were DLCO% and UIP pattern, while at 10 years, dysphagia and DLCO% were significant poor prognosis factors.

**Conclusions** Anti-PL-7 antibodies, dysphagia, UIP pattern, and decreased DLCO% predicted poor outcomes in ARS-ILD, indicating the importance of comprehensive risk assessment.

**Key Points**

- *In patients with ARS-ILD, anti-PL-7 antibodies are associated with risk of all-cause mortality, and evaluation of antibody subtypes in prognosis is important.*
- *The UIP pattern affected prognosis and pulmonary events within the first 5 years.*
- *Dysphagia is the strongest predictor of all-cause mortality and pulmonary events, and management strategies in patients with ARS-ILD are important.*

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Antibodies tar-geting aminoacyl tRNA synthetases (anti-ARS) identify patients with the anti-synthetase syndrome (ASyS), which frequently includes ILD but also may include myositis, arthritis, mechanic's hands, Raynaud phenomenon, and/or fever [8, 9]. There are currently 8 known anti-ARS anti-bodies including anti-Jo-1, -EJ, -PL-7, -PL-12, -KS, -OJ, -Zo, and Ha [8].

Each anti-ARS antibody subtype is associated with different frequencies of clinical manifestations (such as myositis, arthritis, and ILD) as well as variable outcomes [8].

ASyS patients without myosi-tis were diagnosed with ILD in the absence of defined criteria for myositis [9]. ILD was diagnosed by a clinical rheumatologist and pulmonologist based on respiratory symptoms and radiological findings, and was classified usual interstitial pneumonia (UIP), nonspecific intersti-tial pneumonia (NSIP), or organizing pneumonia based on radiological and/or pathological findings by the European Respiratory Society and the American Thoracic Society classification criteria [24–27]. ILD that did not meet the classification criteria described above was defined as an unclassifiable pattern [27]. Pulmonary function tests (PFTs) utilized data from the date closest to the initial rheumatology consultation. Pulmonary events defined as lung transplantation and/or pulmonary death were timed from the first visit rheumatology evaluation as recorded in the University of Pittsburgh database and the patient's chart. In this study, deaths due to lung-related infections such as bacterial pneumonia were classified as other death [28]

Patient had myositis (n = 97), ASyS without myositis (n = 17), or other CTDs (n = 17) including overlap syndrome (n = 9), RA (n = 2), SSc (n = 4), and MCTD (n = 2). Most subjects were female (69%) and 88 (67%) were anti-Jo-1 antibody positive, followed by 5 (4%) with anti-EJ, 14 (11%) with anti-PL-7, 17 (13%) with anti-PL-12, 6 (5%) with anti-KS, and 1 (1%) with anti-OJ antibodies. The relationship between ARS-ILD subgroups and each autoantibody is as follows; myositis with anti-Jo-1 (n = 71), anti-EJ (n = 2), anti-PL-7 (n = 13), anti-PL-12 (n = 7), anti-KS (n = 3), and anti-OJ (n = 1); ASyS without myositis with anti-Jo-1 (n = 9), anti-EJ (n = 2), anti-PL-7 (n = 1), anti-PL-12 (n = 3), and anti-KS (n = 2); other CTDs with anti-Jo-1 (n = 8), anti-EJ (n = 1), anti-PL-12 (n = 7), and anti-KS (n = 1). The frequencies of clinical manifestations were as follows: proximal muscle weakness (74%) was the most common, followed by joint pain/arthritis (66%), mechanic's hands (55%), Raynaud phenomenon (50%), and classic dermatomyositis rashes (heliotrope rash, Gottron papules/sign, V-sign, and/or shawl sign) (34%). Dysphagia (25%), dry eyes (18%), and dry mouth (27%) were also reported. Regarding PFT data, the median and interquartile range (IQR) interval between first visit and PFTs was 10 days (IQR:26–117) days. The median (IQR) FVC% was 64% (50–80), and the median (IQR) diffusing capacity for carbon monoxide (DLCO) % was 50% (40–66), both of which were relatively low. In the classification of ILD, NSIP (69%) and UIP (26%) accounted for the majority. Ninety-nine percent of patients were given glucocorticoids at some point in their disease course while 125 patients also received non-steroid immunosuppressive drug therapy, with or without glucocorticoids, including mycophenolate mofetil (MMF), calcineurin inhibitors, cyclophosphamide, azathioprine (AZA) and methotrexate. Approximately half (47%) of these patients used 3 or more immunosuppressive drugs during the follow-up period. AZA (59%) and MMF (53%) were the most commonly used immunosuppressive agents during the follow-up period.

Overall, 20 patients experienced pulmonary events that encompassed lung-related deaths (n = 9) and/or lung transplants (n = 11). Dur-ing the 10-year observation period, all-cause mortality increased to 28% (n = 37), with half of the 37 deaths (n = 18) attributable to lung-related causes and pulmonary events increased to 24% (n = 32). Lung transplantation was required in 14 patients. During the follow-up period, pulmonary death was the most common cause of death in both the first and last five years, with similar proportions (47% vs 50%). For the distribution of non-pulmonary causes, in the first five years, deaths due to infections (26%), cardiovascular disease (21%), and other specified causes (5%) were observed in order.

**Table 1** Clinical findings of ARS-ILD patients

| | Total patients (n = 131) |
|---|---|
| Age (years) at first visit | 51 ± 13 |
| Age (years) at diagnosis | 49 ± 12 |
| Myositis/ILD without myositis/Other CTDs | 97/17/17 |
| Race (white/black/Asian) | 96/34/1 |
| Male/Female | 40/91 |
| Antibody subtype | |
| Jo-1, no. (%) | 88 (67) |
| EJ, no. (%) | 5 (4) |
| PL-7, no. (%) | 14 (11) |
| PL-12, no. (%) | 17 (13) |
| KS, no. (%) | 6 (5) |
| OJ, no. (%) | 1 (1) |
| Clinical findings | |
| Muscle weakness, no. (%) | 97 (74) |
| Mechanical hands, no. (%) | 72 (55) |
| Classic DM, no. (%) | 45 (34) |
| Raynaud phenomenon, no. (%) | 65 (50) |
| Skin ulcers, no. (%) | 8 (6) |
| Dysphagia, no. (%) | 33 (25) |
| Arthralgia/arthritis, no. (%) | 87 (66) |
| Dry eyes, no. (%) | 23 (18) |
| Dry mouth, no. (%) | 35 (27) |
| Pulmonary function tests[a] | |
| FVC% (%) (IQR) | 64 (50–80) |
| DLCO% (%) (IQR) | 50 (40–66) |
| ILD pattern | |
| UIP pattern, no. (%) | 34 (26) |
| NSIP, no. (%) | 91 (69) |
| OP, no. (%) | 5 (4) |
| Unclassifiable, no. (%) | 1 (1) |
| Treatment[b] | |
| Corticosteroids, no. (%) | 129 (99) |
| Non-steroid immunosuppressive medication[c] | |
| One immunosuppressive treatment, no. (%) | 28 (21) |
| Two immunosuppressive treatments, no. (%) | 36 (28) |
| Three or more immunosuppressive treatments, no. (%) | 61 (47) |
| Immunosuppressive medication used during the follow-up period | |
| MMF, no. (%) | 69 (53) |
| CNIs, no. (%) | 65 (50) |
| CY, no. (%) | 49 (37) |
| AZA, no. (%) | 77 (59) |
| MTX, no. (%) | 58 (44) |
| Additional treatment | |
| IVIG, no. (%) | 15 (12) |
| RTX, no. (%) | 26 (20) |

The values of age are presented as the mean (S.D.) Other values were calculated using the median (IQR)

[a]Out of 131 people, 109 had PFTs done within 2 years of their first visit

[b]Treatment regimen from diagnosis until last visit

[c]Non-steroid immunosuppressive medication includes MMF, CNIs, CY, AZA and MTX

Abbreviations: anti-aminoacyl tRNA synthetase antibody, anti-ARS antibody: ILD, interstitial lung disease: CTDs, connective tissue diseases; DM, dermatomyositis; FVC, forced vital capacity: DLCO, diffusing capacity of carbon monoxide: IQR, interquartile ranges: UIP, usual interstitial pneumonia: NSIP, non-specific interstitial pneumonitis; OP, organizing pneumonia: MMF, mycophenolate mofetil: CNIs, calcineurin inhibitors: CY, cyclophosphamide: AZA, azathioprine: MTX, methotrexate: IVIG, intravenous immunoglobulin: RTX, rituximab

**Table 2** Clinical course and complications

| | Total patients (n = 131) |
|---|---|
| 5-year outcomes (all cause) | |
| All-cause mortality, no. (%) | 19 (15) |
| Pulmonary death, no. (%) | 9 (7) |
| Other death, no. (%) | 10 (8) |
| Infection, no. (%) | 5 (4) |
| Cardiovascular, no. (%) | 4 (3) |
| Others, no. (%) | 1 (1) |
| Pulmonary events, no. (%)[a] | 20 (15) |
| Lung transplantation, no. (%) | 11 (8) |
| 10-year outcomes | |
| All-cause mortality, no. (%) | 37 (28) |
| Pulmonary death, no. (%) | 18 (14) |
| Other death, no. (%) | 19 (15) |
| Infection, no. (%) | 7 (5) |
| Malignancy, no. (%) | 2 (2) |
| Cardiovascular, no. (%) | 4 (3) |
| Others, no. (%) | 6 (5) |
| Pulmonary events, no. (%)[a] | 32 (24) |
| Lung transplantation, no. (%) | 14 (11) |
| Follow-up periods after first visit (years, IQR) | 10.0 (4.8–10.0) |

The values of follow-up periods as the median (IQR)

[a]Lung transplantation and lung-related deaths do not overlap

Abbreviations: IQR, interquartile range

higher rates of pulmonary events over the 10-year observation period were observed in patients with a lower baseline FVC% and DLCO% and a higher incidence of dysphagia (Fig. 1D, Supplementary Table 1).

## Risk factors for all-cause mortality and pulmonary events

Univariate and multivariate analyses for all-cause mortal-ity in patients with ARS-ILD are shown in Table 4. Risk factors (univariate) for death at 5 years were dysphagia, dry eyes, DLCO%, UIP pattern and anti-PL-7 antibody positivity. In a multivariate analysis adjusted for age at first visit/diagnosis and FVC%, dysphagia, dry eyes, UIP pattern, and anti-PL-7 antibody positivity were independ-ent risk factors. Dysphagia and UIP pattern were strongly related with short-term all-cause mortality. Further-more, univariate analyses for 10-year all-cause mortality included baseline age, dysphagia, dry eyes, low DLCO %, and the presence of anti-PL-7 antibody (Table 4). In mul-tivariate analysis, only dysphagia and low DLCO% were independent risk factors, while anti-PL-7 antibody posi-tivity was associated with prognosis only after adjustment for age at first visit and FVC%. As with 5-year all-cause mortality, dysphagia was most associated with 10-year all-cause mortality.

In our study, ILD patients with anti-ARS antibodies were classified into three groups: myositis, ASyS without myositis and other CTDs. Notably, 74% of the ARS-ILD patients in

**Table 3** Clinical differences between surviving and non-surviving patients for 10-years

| | Survivors (n = 94) | Non-survivors (n = 37) | *p*-value |
|---|---|---|---|
| Age (years) at first visit | 49 ± 11 | 55 ± 14 | 0.01 |
| Age (years) at diagnosis | 47 ± 11 | 53 ± 14 | 0.02 |
| Myositis/ILD without myositis/Other CTDs | 71/12/11 | 26/5/6 | 0.77 |
| Race (white/black/Asian) | 70/23/1 | 26/11/0 | 0.69 |
| Male/Female | 30/64 | 10/27 | 0.58 |
| Antibody subtype | | | |
| Jo-1, no. (%) | 66 (70) | 22 (60) | 0.24 |
| EJ, no. (%) | 3 (3) | 2 (5) | 0.44 |
| PL-7, no. (%) | 7 (7) | 7 (19) | 0.06 |
| PL-12, no. (%) | 11 (12) | 6 (16) | 0.33 |
| KS, no. (%) | 6 (6) | 0 (0) | 0.13 |
| OJ, no. (%) | 1 (1) | 0 (0) | 0.71 |
| Clinical findings | | | |
| Muscle weakness, no. (%) | 70 (75) | 27 (73) | 0.86 |
| Mechanical hands, no. (%) | 52 (55) | 20 (54) | 0.90 |
| Classic DM symptoms, no. (%) | 34 (36) | 11 (30) | 0.49 |
| Raynaud syndrome, no. (%) | 46 (49) | 19 (51) | 0.80 |
| Skin ulcers, no. (%) | 4 (4) | 4 (11) | 0.16 |
| Dysphagia, no. (%) | 18 (19) | 15 (41) | 0.01 |
| Arthritis, no. (%) | 65 (70) | 22 (60) | 0.29 |
| Dry eye, no. (%) | 13 (14) | 10 (27) | 0.08 |
| Dry mouth, no. (%) | 24 (26) | 11 (30) | 0.63 |
| Pulmonary function tests[b] | | | |
| FVC% (%) | 68 (50–79) | 58 (45–83) | 0.36 |
| DLCO% (%) | 53 (42–69) | 45 (32–51) | < 0.01 |
| ILD pattern | | | |
| UIP pattern, no. (%) | 20 (21) | 14 (38) | 0.05 |
| NSIP, no. (%) | 69 (73) | 22 (60) | 0.12 |
| OP, no. (%) | 4 (4) | 1 (3) | 0.56 |
| Unclassifiable, no. (%) | 1 (1) | 0 (0) | 0.72 |
| Treatment[b] | | | |
| Corticosteroids, no. (%) | 94 (100) | 35 (95) | 0.08 |
| Non-steroid immunosuppressive medication[c] | | | |
| MMF, no. (%) | 52 (55) | 17 (46) | 0.33 |
| CNIs, no. (%) | 47 (50) | 18 (49) | 0.89 |
| CY, no. (%) | 31 (33) | 18 (49) | 0.10 |
| AZA, no. (%) | 61 (65) | 16 (43) | 0.02 |
| MTX, no. (%) | 45 (48) | 13 (35) | 0.19 |
| Additional treatement | | | |
| IVIG, no. (%) | 13 (14) | 2 (5) | 0.14 |
| RTX, no. (%) | 21 (22) | 5 (14) | 0.25 |
| Follow-up periods after first visit (years, IQR) | 10.0 (9.1–10.0) | 4.8 (3.1–7.6) | < 0.01 |

The values of age are presented as the mean (S.D.) Other values were calculated using the median (IQR). P-values were determined using Student's t-test for analyzing mean values, the Mann–Whitney U test for comparing median values, and chi-square or Fisher's exact tests for categorical variables

[a]Out of 130 people, 109 had PFTs done within 2 years of their first visit

[b]Treatment regimens are defined as treatment for 10-year observation period

[c]Non-steroid immunosuppressive medication used during the follow-up period

Abbreviations: ILD, interstitial lung disease: CTDs, connective tissue diseases; DM, dermatomyositis; FVC, forced vital capacity: DLCO, diffusing capacity of carbon monoxide: UIP, usual interstitial pneumonia: NSIP, non-specific interstitial pneumonitis; OP, organizing pneumonia: MMF, mycophenolate mofetil: CNIs, calcineurin inhibitors: CY, cyclophosphamide: AZA, azathioprine: MTX, methotrexate: IVIG, intravenous immunoglobulin: RTX, rituximab: IQR, interquartile ranges

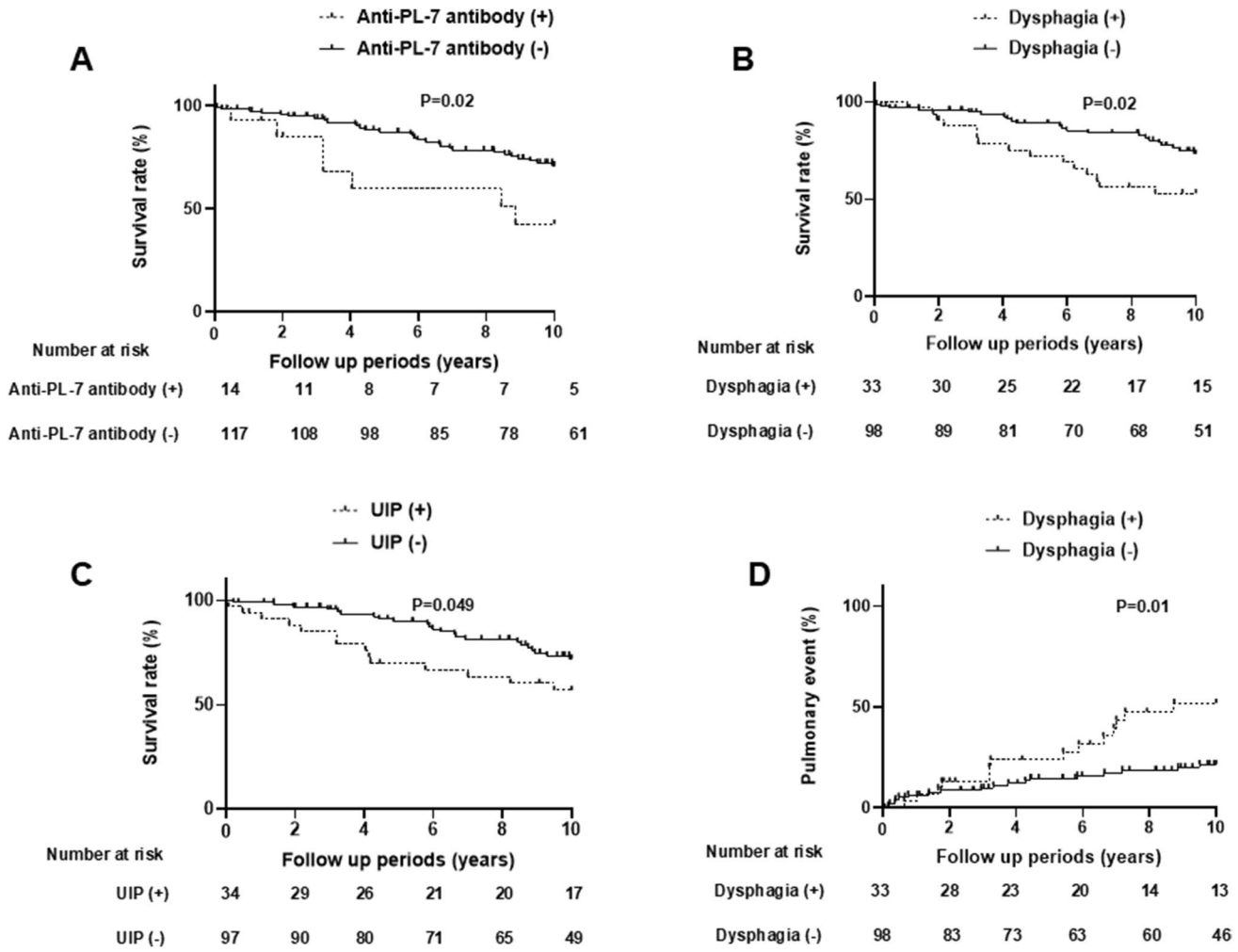


**Fig. 1** Survival rates between patients with ARS-ILD. Survival rates between patients with and without anti- PL-7 antibodies (**A**), dysphagia (**B**) and usual interstitial pneumonia (UIP) (**C**). Pulmonary events between patients with and without dysphagia (**D**)

this study were diagnosed with myositis. A previous study showed that anti-ARS antibodies are often positive in myositis or ASyS without myositis, but are also rarely identified in other CTDs such as SLE, SSc, and RA [31]. Furthermore, our study demonstrated that the proportions of anti-ARS antibody subtypes varied among the three groups of ARS-ILD, with anti-Jo-1 antibodies detected in 73% of patients with myositis, and lower proportions found in ASyS without myositis (53%) and other CTDs (47%). Anti-Jo-1 antibody is the most commonly encountered anti-ARS antibody, and many anti-Jo-1 antibody positive patients develop ILD along with other extra-pulmonary manifestations of ASyS [8, 32]. Additionally, the frequencies of diagnoses such as myositis, ILD alone, and other CTDs differ among the subtypes of anti-ARS antibodies [9].

We reported that the overall mortality rate increased from 15 to 28% between the 5- and 10-year observation periods. For both periods, half of the deaths were respiratory-related. Among patients with myositis associated ILD, anti-ARS antibody-positive patients are known to have a better prognosis than negative patients [33–35]. On the other hand, in a long-term observation in Japan, 7 (19.4%) deaths or transplants were confirmed in 36 patients with ARS-ILD over a median period of 72.4 ± 22.7 months [12]. Therefore, we always need long-term observational studies in patients with ARS-ILD.

**Table 4** Baseline prognosis factors in ARS-ILD patients for mortality

| | Unadjusted HR | 95% CI | *p*-value | | Age (at first visit)- and FVC% (at first visit)—adjusted HR | 95% CI | *p*-value | Age (at diagnosis)- and FVC% (at first visit)- adjusted HR | 95% CI | *p*-value |
|---|---|---|---|---|---|---|---|---|---|---|
| Univariate | | | | Multivariate | | | | | | |
| 5-year all cause death | | | | | | | | | | |
| Age (at first visit) | 1.04 | 1.00–1.08 | 0.08 | | - | - | - | - | - | - |
| Age (at diagnosis) | 1.04 | 1.00–1.08 | 0.07 | | - | - | - | - | - | - |
| Black (vs white) | 0.75 | 0.24–2.18 | 0.57 | | - | - | - | - | - | - |
| Male (vs Female) | 0.39 | 0.11–1.33 | 0.13 | | - | - | - | - | - | - |
| ILD without myositis (vs myositis) | 1.33 | 0.37–4.70 | 0.66 | | - | - | - | - | - | - |
| Other CTDs (vs myositis) | 1.94 | 0.62–6.00 | 0.25 | | - | - | - | - | - | - |
| Dysphagia | 2.72 | 1.11–6.71 | 0.03 | | 4.04 | 1.48–11.0 | 0.01 | 4.88 | 1.69–14.1 | < 0.01 |
| Dry eye | 3.11 | 1.22–7.90 | 0.02 | | 3.62 | 1.31–9.96 | 0.01 | 3.43 | 1.24–9.51 | 0.02 |
| Dry mouth | 1.32 | 0.50–3.47 | 0.58 | | - | - | - | - | - | - |
| FVC% (at first visit) | 0.98 | 0.96–1.01 | 0.17 | | - | - | - | - | - | - |
| DLCO% (at first visit) | 0.97 | 0.94–1.00 | 0.046 | | 0.97 | 0.94–1.01 | 0.10 | 0.97 | 0.94–1.01 | 0.09 |
| UIP pattern | 3.45 | 1.40–8.49 | 0.01 | | 4.40 | 1.65–11.8 | < 0.01 | 4.40 | 1.64–11.8 | < 0.01 |
| Autoantibodies | | | | | | | | | | |
| Jo-1 | 0.41 | 0.17–1.01 | 0.05 | | - | - | - | - | - | - |
| PL-7 | 3.80 | 1.37–10.6 | 0.01 | | 4.25 | 1.29–14.0 | 0.02 | 3.78 | 1.12–12.9 | 0.03 |
| PL-12 | 1.15 | 0.34–3.95 | 0.82 | | - | - | - | - | - | - |
| 10-year all cause death | | | | | | | | | | |
| Age (at first visit) | 1.04 | 1.01–1.07 | 0.02 | | - | - | - | - | - | - |
| Age (at diagnosis) | 1.03 | 1.00–1.06 | 0.03 | | - | - | - | - | - | - |
| Black (vs white) | 1.19 | 0.59–2.41 | 0.62 | | - | - | - | - | - | - |
| Male (vs Female) | 0.70 | 0.34–1.45 | 0.34 | | - | - | - | - | - | - |
| ILD without myositis (vs myositis) | 0.97 | 0.37–2.54 | 0.96 | | - | - | - | - | - | - |
| Oher CTDs (vs myositis) | 1.38 | 0.57–3.34 | 0.48 | | - | - | - | - | - | - |
| Dysphagia | 2.21 | 1.15–4.27 | 0.02 | | 3.45 | 1.66–7.16 | < 0.01 | 3.92 | 1.83–8.38 | < 0.01 |
| Dry eye | 2.15 | 1.04–4.43 | 0.04 | | 2.17 | 1.01–4.66 | 0.05 | 2.12 | 0.99–4.56 | 0.05 |
| Dry mouth | 1.13 | 0.56–2.28 | 0.74 | | - | - | - | - | - | - |
| FVC% (at first visit) | 0.99 | 0.98–1.01 | 0.35 | | - | - | - | - | - | - |

**Table 4** (continued)

| | Unadjusted HR | 95% CI | *p*-value | Age (at first visit)- and FVC% (at first visit)—adjusted HR | 95% CI | *p*-value | Age (at diagnosis)- and FVC% (at first visit)- adjusted HR | 95% CI | *p*-value |
|---|---|---|---|---|---|---|---|---|---|
| DLCO% (at first visit) | 0.97 | 0.95–0.99 | < 0.01 | 0.96 | 0.94–0.99 | < 0.01 | 0.96 | 0.94–0.99 | < 0.01 |
| UIP pattern | 1.93 | 0.99–3.75 | 0.05 | - | - | - | - | - | - |
| Autoantibodies | | | | | | | | | |
| Jo-1 | 0.68 | 0.35–1.32 | 0.25 | - | - | - | - | - | - |
| PL-7 | 2.65 | 1.16–6.05 | 0.02 | 2.68 | 1.04–6.93 | 0.04 | 2.54 | 0.97–6.65 | 0.06 |
| PL-12 | 1.16 | 0.48–2.77 | 0.74 | - | - | - | - | - | - |

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval;
anti-aminoacyl tRNA synthetase antibody, anti-ARS antibody: ILD, interstitial lung disease: CTDs, connective tissue diseases;
FVC, forced vital capacity: DLCO, diffusing capacity of carbon monoxide: UIP, usual interstitial pneumonia

In this study, various risk factors for mortality and pulmonary events were identified. First, autoantibodies were a risk factor in all-cause mortality. In our study, most patients positive for anti-PL-7 antibody who died were identified within the first five years. After 5 years of observation, anti-PL-7 antibody positivity was associated with poor prognostic factor. In terms of autoantibody subtypes, anti-PL-12 and anti-PL-7 antibodies in ASyS patients were associated with severe ILD in a North American study [15]. A Chinese study examining the characteristics of different ARS antibodies also found that anti-PL-7 antibody was associated with progressive ILD and showed a more rapid decline in survival rates within the first year of onset compared to other autoantibodies [36]. Therefore, a high index of suspicion and an accurate and timely serological profile is critical in patients presenting with ARS-ILD. In addition, our findings indicate that dysphagia was associated with 5-year and 10-year mortality as well as 10-year pulmonary events. IIM patients with dysphagia had significantly lower cumulative survival than those without [37, 38]. Our study demonstrated an association with pulmonary events, whereas some previous studies have reported a relationship between reflux/dysphagia and ILD progression in SSc [39, 40]. Moreover, our study identified declines in respiratory functional parameters (FVC% and DLCO%) as poor prognostic factors. Similarly, a previous study identified lower FVC as an independent poor prognostic factor in myositis patients with ILD [29]. Our findings indicate that the UIP pattern was also associated with poor prognosis among patients with ARS-ILD, though previous study investigating myositis-related UIP (myositis-UIP) have shown a better prognosis in myositis-UIP compared to IPF [28]. Overall, our study suggests that a combination of clinical features, autoantibody subtype, pulmonary function parameters, and ILD pattern results may influence prognosis.

This retrospective, single center study had some limitations; Since 67% of our patients are positive for anti-Jo-1 antibody, we need to collect more patients to understand the details of the clinical course of non-Jo-1 antibody. In addition, the enrolled patients may have received various therapeutic interventions during the follow-up period, which may have affected their prognosis. Furthermore, many patients in this study used three or more non-steroidal immunosuppressants during the follow-up period, but the exact order and duration of their use could not be tracked. This study used data from a long-term registry collected over a 30-year period. While this provides an evaluation of long-term outcomes, there may be some limitations, such as missing data, changes in diagnostic criteria, and variability in measurements over time. However, the strength of this study's design was that it was based on prospectively

**Table 5** Risk factors of pulmonary event in ARS-ILD patients

| | Unadjusted HR | 95% CI | *p*-value | Age (at first visit)- and FVC% (at first visit)- adjusted HR | 95% CI | *p*-value | Age (at diagnosis)-and FVC% (at first visit)- adjusted HR | 95% CI | *p*-value |
|---|---|---|---|---|---|---|---|---|---|
| Univariate | | | | Multivariate | | | | | |
| 5-year pulmonary event | | | | | | | | | |
| Age (at first visit) | 1.03 | 0.99–1.07 | 0.19 | - | - | - | - | - | - |
| Age (at diagnosis) | 1.02 | 0.98–1.05 | 0.43 | - | - | - | - | - | - |
| Black (vs White) | 0.68 | 0.23–2.03 | 0.49 | - | - | - | - | - | - |
| Male (vs Female) | 0.93 | 0.36–2.41 | 0.88 | - | - | - | - | - | - |
| ILD without myositis (vs myositis) | 1.96 | 0.63–6.09 | 0.24 | - | - | - | - | - | - |
| Other CTDs (vs myositis) | 2.12 | 0.68–6.57 | 0.19 | - | - | - | - | - | - |
| Dysphagia | 1.56 | 0.62–3.91 | 0.34 | - | - | - | - | - | - |
| Dry eye | 1.22 | 0.41–3.66 | 0.72 | - | - | - | - | - | - |
| Dry mouth | 1.21 | 0.46–3.14 | 0.70 | - | - | - | - | - | - |
| FVC% | 0.97 | 0.94–0.99 | 0.01 | - | - | - | - | - | - |
| DLCO% | 0.94 | 0.91–0.98 | < 0.01 | 0.95 | 0.91–0.99 | 0.01 | 0.94 | 0.91–0.99 | 0.01 |
| UIP pattern | 2.79 | 1.16–6.74 | 0.02 | 4.31 | 1.67–11.1 | < 0.01 | 4.24 | 1.64–11.0 | < 0.01 |
| Autoantibodies | | | | | | | | | |
| Jo-1 | 0.72 | 0.30–1.77 | 0.48 | - | - | - | - | - | - |
| PL-7 | 2.49 | 0.83–7.47 | 0.10 | - | - | - | - | - | - |
| PL-12 | 1.49 | 0.50–4.46 | 0.48 | - | - | - | - | - | - |
| 10-year pulmonary event | | | | | | | | | |
| Age (at first visit) | 1.02 | 0.99–1.05 | 0.34 | - | - | - | - | - | - |
| Age (at diagnosis) | | | | - | - | - | - | - | - |
| Black (vs White) | 0.63 | 0.26–1.54 | 0.32 | - | - | - | - | - | - |
| Male (vs Female) | 1.07 | 0.51–2.22 | 0.86 | - | - | - | - | - | - |
| ILD without myositis (vs myositis) | 0.98 | 0.34–2.82 | 0.96 | - | - | - | - | - | - |
| Other CTDs (vs myositis) | 1.46 | 0.55–3.83 | 0.45 | - | - | - | - | - | - |
| Dysphagia | 2.43 | 1.21–4.89 | 0.01 | 2.60 | 1.22–5.51 | 0.01 | 2.69 | 1.25–5.78 | 0.01 |
| Dry eye | 1.19 | 0.49–2.89 | 0.71 | - | - | - | - | - | - |
| Dry mouth | 0.89 | 0.40–1.98 | 0.77 | - | - | - | - | - | - |
| FVC% | 0.98 | 0.96–0.99 | 0.01 | - | - | - | - | - | - |
| DLCO% | 0.95 | 0.93–0.98 | < 0.01 | 0.95 | 0.92–0.98 | < 0.01 | 0.94 | 0.92–0.98 | < 0.01 |
| UIP pattern | 1.84 | 0.89–3.82 | 0.10 | - | - | - | - | - | - |
| Autoantibodies | | | | | | | | | |
| Jo-1 | 0.93 | 0.45–1.94 | 0.86 | - | - | - | - | - | - |
| PL-7 | 2.02 | 0.77–5.25 | 0.15 | - | - | - | - | - | - |
| PL-12 | 1.07 | 0.41–2.78 | 0.89 | - | - | - | - | - | - |

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval;

anti-aminoacyl tRNA synthetase antibody, anti-ARS antibody: ILD, interstitial lung disease: CTDs, connective tissue diseases;

FVC, forced vital capacity: DLCO, diffusing capacity of carbon monoxide: UIP, usual interstitial pneumonia

collected data over a long-time period. Moreover, this is one of the larger North American cohorts of ARS-ILD with data on prognostic factors for pulmonary events and all-cause mortality.

In conclusion, we evaluated the clinical course of ARS-ILD patients in North American patients in the majority of our study subjects. Our study identified different risk factors for all-cause mortality and pulmonary events. For all-cause mortality, it was important to evaluate the subtype of anti-ARS antibodies, especially anti-PL-7 antibodies, which showed a higher risk of death. Furthermore, over a 5-year period, evaluation of UIP pattern had an impact on prognosis. Interestingly, at 10 years, UIP pattern did not affect prognosis. This result may suggest that patients with UIP patterns may not be expected to have a long survival and that additional treatment should be considered when confirmed. Dysphagia is the most important risk factor for all-cause mortality and pulmonary events, and its management in these patients will be important in future studies.

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## References

1. Ernste FC, Reed AM (2013) Idiopathic inflammatory myopathies: current trends in pathogenesis, clinical features, and up-to-date treatment recommendations Mayo Clinic Proceedings Elsevier, pp 83–105
2. Khoo T, Lilleker JB, Thong BY-H, Leclair V, Lamb JA, Chinoy H (2023) Epidemiology of the idiopathic inflammatory myopathies. Nat Rev Rheumatol 19:695–712
3. Nuño-Nuño L, Joven BE, Carreira PE et al (2017) Mortality and prognostic factors in idiopathic inflammatory myositis: a retrospective analysis of a large multicenter cohort of Spain. Rheumatol Int 37:1853–1861
4. Marie I (2012) Morbidity and mortality in adult polymyositis and dermatomyositis. Curr Rheumatol Rep 14:275–285
5. Hallowell RW, Paik JJ (2021) Myositis-associated interstitial lung disease: a comprehensive approach to diagnosis and management. Clin Exp Rheumatol 40:373
6. Hengstman GJ, van Engelen BG, van Venrooij WJ (2004) Myositis specific autoantibodies: changing insights in pathophysiology and clinical associations. Curr Opin Rheumatol 16:692–699
7. Connolly CM, Gupta L, Fujimoto M, Machado PM, Paik JJ (2024) Idiopathic inflammatory myopathies: current insights and future frontiers. The Lancet Rheumatol 6:e115–e127
8. Huang K, Aggarwal R (2020) Antisynthetase syndrome: a distinct disease spectrum. J Scleroderma Related Disord 5:178–191
9. Hamaguchi Y, Fujimoto M, Matsushita T et al (2013) Common and distinct clinical features in adult patients with anti-aminoacyl-tRNA synthetase antibodies: heterogeneity within the syndrome. PLoS ONE 8:e60442
10. Zhan X, Yan W, Wang Y et al (2021) Clinical features of antisynthetase syndrome associated interstitial lung disease: a retrospective cohort in China. BMC Pulm Med 21:1–9
11. Watanabe K, Handa T, Tanizawa K et al (2011) Detection of antisynthetase syndrome in patients with idiopathic interstitial pneumonias. Respir Med 105:1238–1247
12. Tanizawa K, Handa T, Nakashima R et al (2017) The long-term outcome of interstitial lung disease with anti-aminoacyl-tRNA synthetase antibodies. Respir Med 127:57–64
13. Rojas-Serrano J, Herrera-Bringas D, Mejía M, Rivero H, Mateos-Toledo H, Figueroa JE (2015) Prognostic factors in a cohort of antisynthetase syndrome (ASS): serologic profile is associated with mortality in patients with interstitial lung disease (ILD). Clin Rheumatol 34:1563–1569
14. Zhao N, Jiang W, Wu H et al (2022) Clinical features, prognostic factors, and survival of patients with antisynthetase syndrome and interstitial lung disease. Front Immunol 13:872615
15. Pinal-Fernandez I, Casal-Dominguez M, Huapaya JA et al (2017) A longitudinal cohort study of the anti-synthetase syndrome: increased severity of interstitial lung disease in black patients and patients with anti-PL7 and anti-PL12 autoantibodies. Rheumatology 56:999–1007
16. Wilfong EM, Young-Glazer JJ, Sohn BK et al (2022) Anti-tRNA synthetase syndrome interstitial lung disease: a single center experience. Respir Med 191:106432
17. Bohan A, Peter JB (1975) Polymyositis and dermatomyositis. N Engl J Med 292:344–347
18. Hochberg MC (1997) Updating the American College of rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 40:1725–1725
19. Masi AT, Diagnostic SFSCotARA, Committee TC (1980) Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum 23: 581-590
20. van den Hoogen F, Khanna D, Fransen J et al (2013) Classification criteria for systemic sclerosis: an ACR-EULAR collaborative initiative. Arthritis Rheum 65:2737
21. Arnett FC, Edworthy SM, Bloch DA et al (1988) The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum: Official J Am College Rheumatol 31:315–324
22. Sharp GC (1987) Diagnostic criteria for classification of MCTD. In: Kasukawa R, Sharp GC (eds) Mixed Connective Tissue Disease and Antinuclear Autoantibodies. Elsevier, Amsterdam, pp 23–32

23. Aguila LA, Lopes MRU, Pretti FZ et al (2014) Clinical and laboratory features of overlap syndromes of idiopathic inflammatory myopathies associated with systemic lupus erythematosus, systemic sclerosis, or rheumatoid arthritis. Clin Rheumatol 33:1093–1098
24. Travis WD, Costabel U, Hansell DM et al (2013) 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 188:733–748
25. Raghu G, Remy-Jardin M, Myers JL et al (2018) Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med 198:e44–e68
26. Society ER, Society AT (2002) American thoracic society. Am J Respir Crit Care Med 165:277–304
27. Zamora AC, Hoskote SS, Abascal-Bolado B et al (2016) Clinical features and outcomes of interstitial lung disease in anti-Jo-1 positive antisynthetase syndrome. Respir Med 118:39–45
28. Aggarwal R, McBurney C, Schneider F et al (2017) Myositis-associated usual interstitial pneumonia has a better survival than idiopathic pulmonary fibrosis. Rheumatology 56:384–389
29. Fujisawa T, Hozumi H, Kono M et al (2014) Prognostic factors for myositis-associated interstitial lung disease. PLoS ONE 9:e98824
30. Obert J, Freynet O, Nunes H et al (2016) Outcome and prognostic factors in a French cohort of patients with myositis-associated interstitial lung disease. Rheumatol Int 36:1727–1735
31. Nakashima R, Imura Y, Hosono Y et al (2014) The multicenter study of a new assay for simultaneous detection of multiple anti-aminoacyl-tRNA synthetases in myositis and interstitial pneumonia. PLoS ONE 9:e85062
32. Lega J-C, Reynaud Q, Belot A, Fabien N, Durieu I, Cottin V (2015) Idiopathic inflammatory myopathies and the lung. Eur Respir Rev 24:216–238
33. Hozumi H, Enomoto N, Kono M et al (2015) Prognostic significance of anti-aminoacyl-tRNA synthetase antibodies in polymyositis/dermatomyositis-associated interstitial lung disease: a retrospective case control study. PLoS ONE 10:e0120313
34. Sato S, Masui K, Nishina N et al (2018) Initial predictors of poor survival in myositis-associated interstitial lung disease: a multicentre cohort of 497 patients. Rheumatology 57:1212–1221
35. Chen F, Li S, Wang T, Shi J, Wang G (2018) Clinical heterogeneity of interstitial lung disease in polymyositis and dermatomyositis patients with or without specific autoantibodies. Am J Med Sci 355:48–53
36. Shi J, Li S, Yang H et al (2017) Clinical profiles and prognosis of patients with distinct antisynthetase autoantibodies. J Rheumatol 44:1051–1057
37. Dankó K, Ponyi A, Constantin T, Borgulya G, Szegedi G (2004) Long-term survival of patients with idiopathic inflammatory myopathies according to clinical features: a longitudinal study of 162 cases. Medicine 83:35–42
38. Bai Z, Shen G, Dong L (2021) Analysis of risk factors of interstitial lung disease and mortality rates in Chinese patients with idiopathic inflammatory myopathy. Int J Rheum Dis 24:815–827
39. Hoffmann-Vold A-M, Allanore Y, Alves M et al (2021) Progressive interstitial lung disease in patients with systemic sclerosis-associated interstitial lung disease in the EUSTAR database. Ann Rheum Dis 80:219–227
40. Zhang XJ, Bonner A, Hudson M, Baron M, Pope J, Group CSR (2013) Association of gastroesophageal factors and worsening of forced vital capacity in systemic sclerosis. J Rheumatol 40: 850-858