Association between autoantibodies and interstitial lung disease in autoimmune disease patients: a retrospective study

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Abstract

Objective

This study aimed to investigate the relationship between specific autoantibodies, particularly anti-Ro52, and the development of interstitial lung disease (ILD) in patients with autoimmune diseases (AID), with the goal of identifying potential biomarkers for the early detection and management of ILD.

Methods

A retrospective cohort study was conducted at Peking Union Medical College Hospital, involving 2,021 AID patients who underwent antinuclear antibody (ANA) testing between 2017 and 2019. Clinical and serological data were collected to assess the presence of ILD and its association with specific autoantibodies. Least absolute shrinkage and selection operator (LASSO) regression was used to identify predictors of ILD.

Results

Among the 2,021 patients, ILD prevalence varied across AID subgroups, with the highest rates observed in idiopathic inflammatory myopathies (IIM), overlap syndrome, and systemic sclerosis. Anti-Ro52 was significantly more frequent in IIM patients with ILD compared to those without ILD (83.0% vs. 37.8%, $p<0.0001$). Anti-RNP was detected at a significantly higher rate in lupus-ILD patients. Additionally, positivity rates of anti-SSA/Ro60 and anti-CENP B were inversely associated with ILD in Sjögren's disease and systemic sclerosis, respectively. LASSO regression analysis identified anti-Ro52, age, and anti-MDA5 as significant predictors of ILD development in IIM. Anti-Ro52 positivity was associated with a more than two-fold increased risk of ILD progression in mixed connective tissue disease.

Conclusion

Anti-Ro52, together with age and anti-MDA5, was identified as a significant predictor of ILD in IIM patients. This study highlights the potential of autoantibodies as biomarkers for early detection and management of ILD in AID patients.

Key words

interstitial lung disease, autoimmune diseases, anti-Ro52, idiopathic inflammatory myopathies

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Introduction

Autoimmune diseases (AID) encompass a wide range of disorders in which the immune system erroneously attacks the body's own tissues, resulting in chronic inflammation and potential organ damage (1). Interstitial lung disease (ILD) is the most common lung manifestation in AID and often presents as the initial symptom, involving a group of pulmonary disorders that affect the alveolar tissue and space, leading to progressive respiratory failure and impaired lung function (2-4). ILD can be broadly categorised into idiopathic, autoimmune-related, exposure-related (including iatrogenic), cystic or airspace-filling diseases, sarcoidosis, and rare conditions. Idiopathic and secondary ILD often share overlapping radiological-histopathological patterns, most commonly usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP), and organising pneumonia (3). Patients with AID, particularly those with systemic sclerosis (SSc), rheumatoid arthritis (RA), idiopathic inflammatory myopathies (IIM) – including poly-myositis (PM), dermatomyositis (DM), antisynthetase syndrome (ASS), and immune-mediated necrotising myopathy (IMNM) – mixed connective tissue disease (MCTD), and Sjögren's disease (SjD), are at an increased risk of developing ILD, which can adversely impact their long-term prognosis (5).

While the association between AID and ILD is well recognised, the specific underlying mechanisms and reliable biomarkers for predicting ILD in different AID subgroups remain inadequately understood. Previous research has suggested that certain autoantibodies, notably anti-Ro52, may be linked to the presence of ILD in these patients; however, their precise role and clinical utility have yet to be fully established (6-8). Furthermore, the prevalence and impact of anti-Ro52 and other autoantibodies vary across AID subgroups (9), emphasising the need for a deeper exploration of their potential diagnostic and prognostic value.

The objective of this study is to investigate the relationship between specific autoantibodies, particularly anti-Ro52, and the occurrence of ILD in AID patients, aiming to identify biomarkers that could enhance early detection and management of ILD.

Methods

Study cohort and data collection

This retrospective, single-centre observational study was conducted at Peking Union Medical College Hospital. Between January 2017 and December 2019, we screened 91,243 hospitalised patients who underwent antinuclear antibody (ANA) testing. A total of 2,021 patients were included if they met the following criteria: 1. positivity for ANA screening and/or disease-specific autoantibodies, and 2. fulfillment of established classification criteria for the respective autoimmune systemic disease requiring admission to the Department of Rheumatology or the Department of Respiratory Medicine.

All AID diagnoses were established by experienced rheumatologists according to internationally accepted classification criteria, including the ACR/EULAR 2010 criteria for rheumatoid arthritis, the 2016 ACR/EULAR criteria for Sjögren's disease, the 2017 EULAR/ACR criteria for idiopathic inflammatory myopathies, and corresponding classification criteria for other autoimmune systemic diseases. Patients classified as having overlap syndrome fulfilled the classification criteria for more than one autoimmune systemic disease. ILD was diagnosed by pulmonologists based on characteristic findings on high-resolution computed tomography (HRCT).

Multidisciplinary discussion involving rheumatologists, pulmonologists, and radiologists was conducted when necessary. Only hospitalised patients were included to ensure the availability of comprehensive and standardised clinical, radiological, and laboratory data necessary for accurate ILD assessment, as outpatient records often lacked sufficient ILD-related detail. Clinical and laboratory data were retrieved from electronic medical records, including demographics (age and sex), autoantibody profiles, and ILD status. Data on clinical outcomes were also collected, including ILD-related non-elective hospitalisations, forced vital capacity (FVC) percent of predicted value, lung

Table I. Clinical and serological features of patients with autoimmune disease.

	SjD	IIM	SLE	RA	SSc	AAV	MCTD	OS	*p*-value
n	268	180	736	145	69	116	115	60	NA
Age, mean ± SD	53.16±15.14	48.83±14.52	36.81±14.81	57.25± 3.08	52.71±17.52	53.97±18.58	47.3±16.89	45.98±14.11	<0.0001
Female, n (%)	229 (85.4)	122 (67.8)	642 (87.2)	108 (74.5)	58 (84.1)	58 (50.0)	86 (74.8)	53 (88.3)	<0.0001
ILD, n (%)	58 (21.6)	135 (75.0)	58 (7.9)	41 (28.3)	48 (69.6)	39 (33.6)	29 (25.2)	44 (73.3)	<0.0001
ANA, n (%)	188 (70.1)	107 (59.4)	634 (86.1)	83 (57.2)	66 (95.7)	43 (37.1)	96 (83.5)	55 (91.7)	<0.0001
SSA/Ro60, n (%)	216 (80.6)	43 (23.9)	418 (56.8)	31 (21.4)	17 (24.6)	11 (9.5)	38 (33.0)	25 (41.7)	<0.0001
Ro 52, n (%)	224 (83.6)	129 (71.7)	421 (57.2)	35 (24.1)	32 (46.4)	23 (19.8)	59 (51.3)	44 (73.3)	<0.0001
dsDNA-CLIA, n (%)	15 (5.6)	3 (1.7)	285 (38.7)	7 (4.8)	7 (10.1)	4 (3.4)	7 (6.1)	5 (8.3)	<0.0001
PCNA, n (%)	1 (0.4)	1 (0.6)	12 (1.6)	2 (1.4)	1 (1.4)	2 (1.7)	4 (3.5)	2 (3.3)	0.329
ANuA, n (%)	4 (1.5)	1 (0.6)	180 (24.5)	4 (2.8)	3 (4.3)	1 (0.9)	2 (1.7)	3 (5.0)	<0.0001
SSB, n (%)	76 (28.4)	5 (2.8)	76 (10.3)	4 (2.8)	3 (4.3)	4 (3.4)	9 (7.8)	6 (10.0)	<0.0001
PM-Scl, n (%)	5 (1.9)	3 (1.7)	15 (2.0)	1 (0.7)	1 (1.4)	3 (2.6)	0 (0)	2 (3.3)	0.6981
CENP B, n (%)	30 (11.2)	7 (3.9)	27 (3.7)	8 (5.5)	19 (27.5)	3 (2.6)	11 (9.6)	7 (11.7)	<0.0001
AHA, n (%)	8 (3.0)	3 (1.7)	217 (29.5)	3 (2.1)	5 (7.2)	4 (3.4)	4 (3.5)	4 (6.7)	<0.0001
RNP, n (%)	16 (6.0)	9 (5.0)	287 (39.0)	3 (2.1)	15 (21.7)	1 (0.9)	25 (21.7)	27 (45.0)	<0.0001
Sm, n (%)	4 (1.5)	1 (0.6)	126 (17.1)	1 (0.7)	1 (1.4)	1 (0.9)	4 (3.5)	4 (6.7)	<0.0001
Scl-70, n (%)	4 (1.5)	3 (1.7)	13 (1.8)	2 (1.4)	22 (31.9)	0 (0)	1 (0.9)	6 (10.0)	<0.0001
Jo-1, n (%)	4 (1.5)	10 (5.6)	6 (0.8)	4 (2.8)	1 (1.4)	2 (1.7)	0 (0)	6 (10.0)	<0.0001
rRNP, n (%)	12 (4.5)	4 (2.2)	190 (25.8)	3 (2.1)	0 (0)	1 (0.9)	3 (2.6)	2 (3.3)	<0.0001

Data are presented as frequency (percentage) for categorical variables and mean ± standard deviation (SD) for continuous variables. P-values were calculated using the Chi-squared test or Fisher's exact test for categorical variables and the Kruskal-Wallis test for comparisons of continuous variables among multiple groups.
SjD: Sjögren's disease; IIM: idiopathic inflammatory myopathies; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; SSc: systemic sclerosis; AAV: anti-neutrophil cytoplasmic antibody-associated vasculitis; MCTD: mixed connective tissue disease; OS: overlap syndrome; n: number; SD: standard deviation; ILD: interstitial lung disease; ANA: antinuclear antibody; SSA/Ro60: anti-SSA/Ro60 antibody; Ro 52: anti-Ro52 antibody; dsDNA-CLIA: double-stranded DNA-chemiluminescent immunoassay; PCNA: anti-proliferating cell nuclear antigen antibody; ANuA: anti-nucleosome antibody; SSB: anti-SSB antibody; PM-Scl: anti-PM-Scl antibody; CENP B: anti-centromere protein B antibody; AHA: anti-histone antibody; RNP: anti-ribonucleoprotein antibody; Sm: anti-Sm antibody; Scl-70: anti-Scl-70 antibody; Jo-1: anti-Jo-1 antibody; rRNP: anti-ribosomal RNP antibody.

transplantation, and all-cause mortality. Given the retrospective nature of the study and the inpatient-based cohort, follow-up data were obtained from hospital records during routine clinical care. The study protocol was approved by the Ethics Review Committee of Peking Union Medical College Hospital (project no. JS-2156).

Detection of autoantibodies

Indirect immunofluorescence assay (EUROIMMUN AG, Germany) was used for ANA screening, and immunoblotting detection (EUROIMMUN AG, Germany) was employed for specific autoantibodies. Anti-dsDNA was measured using indirect immunofluorescence assay (EUROIMMUN AG, Germany) and enzyme-linked immunosorbent assay (EUROIMMUN AG, Germany). All assays were performed according to the manufacturer's instructions. Myositis antibody profiles – including anti-Jo-1, anti-PL7, anti-PL12, anti-EJ, anti-OJ, anti-Ku, anti-PM-Scl75, anti-PM-Scl100, anti-Mi-2, anti-MDA5, anti-SRP, anti-SAE1, anti-NXP2, and anti-TIF1γ – were retrieved from the patients' medical records.

LASSO regression

Variable selection was performed using Least Absolute Shrinkage and Selection Operator (LASSO) regression with binomial deviance minimisation. All continuous predictors were standardised (z-score transformation) to ensure comparability of coefficient magnitudes. The optimal regularisation parameter (λ) was determined via 10-fold cross-validation using the one-standard-error rule (λ.1se), selecting the most parsimonious model within one standard error of minimum cross-validated deviance. Variables with non-zero coefficients were retained and ranked by absolute coefficient magnitude. Final model performance was assessed through repeated 10-fold cross-validation (3 repetitions), reporting area under the receiver operating characteristic curve (AUC) and Bayesian information criterion (BIC). All analyses were performed in R using the glmnet, pROC, caret, and ggplot2 packages.

Outcome measures

The primary outcomes were ILD progression and all-cause mortality. ILD progression was defined as the occurrence of any of the following: 1. non-elective hospitalisation due to ILD; 2. an absolute decline in forced vital capacity (FVC) percent of predicted value ≥10% from baseline; 3. lung transplantation. Hospitalisation due to ILD was defined as admission for respiratory failure primarily attributed to an ILD exacerbation. ILD progression-free survival was calculated as the time from the first visit with an ILD diagnosis to either ILD progression, death, or the end of study follow-up, whichever occurred first.

Statistical analysis

Data are presented as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on the distribution of the data. The unpaired Mann-Whitney U-test was used for comparisons between two independent groups. For multiple group comparisons, the Kruskal-Wallis test was applied. The Chi-squared test or Fisher's exact test was employed for categorical data analysis. Logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) to assess the risk of ILD development. Ad-

Table II. Clinical and serological features of autoimmune disease patients with and without ILD.

	SjD n=268			IIM n=180			SLE n=736			SSc n=69		
	ILD (+)	ILD (-)	*p*-value	ILD (+)	ILD (-)	*p*-value	ILD (+)	ILD (-)	*p*-value	ILD (+)	ILD (-)	*p*-value
n	58	210	NA	135	45	NA	58	678	NA	48	21	NA
Age, mean ± SD	59.38±13.32	51.45±15.19	0.0002	51.64±13.38	40.4±14.67	<0.0001	46±12.96	36.02±14.70	<0.0001	54.15±17.21	49.43±18.23	0.2916
Female, n (%)	50 (86.2)	179 (85.2)	0.8531	95 (70.4)	27 (60.0)	0.1973	51 (87.9)	591 (87.2)	0.8673	41 (85.4)	17 81)	0.6411
ANA, n (%)	50 (86.2)	192 (91.4)	0.2343	77 (57.0)	30 (66.7)	0.2545	53 (91.4)	581 (85.7)	0.229	47 (97.9)	19 (90.5)	0.1632
SSA/Ro60, n (%)	38 (65.5)	178 (84.8)	0.001	38 (28.1)	5 (11.1)	0.0203	35 (60.3)	383 (56.5)	0.5694	12 (25)	5 (23.8)	0.9159
Ro 52, n (%)	50 (86.2)	174 (82.9)	0.5421	112 (83.0)	17 (37.8)	<0.0001	39 (67.2)	382 (56.3)	0.1074	21 (43.8)	11 (52.4)	0.5083
dsDNA-CLIA, n (%)	3 (5.2)	12 (5.7)	0.8737	1 (0.7)	2 (4.4)	0.0928	17 (29.3)	268 (39.5)	0.1252	5 (10.4)	2 (9.5)	0.91
PCNA, n (%)	0 (0)	1 (0.5)	0.5985	0 (0)	1 (2.2)	0.0824	0 (0)	12 (1.8)	0.307	1 (2.1)	0 (0)	0.5052
ANuA, n (%)	2 (3.4)	2 (1)	0.1652	0 (0)	1 (2.2)	0.0824	11 (19)	169 (24.9)	0.3107	3 (6.2)	0 (0)	0.2414
SSB, n (%)	15 (25.9)	61 (29)	0.6338	4 (3.0)	1 (2.2)	0.7934	7 (12.1)	69 (10.2)	0.6495	2 (4.2)	1 (4.8)	0.9112
PM-Scl, n (%)	2 (3.4)	3 (1.4)	0.3143	2 (1.5)	1 (2.2)	0.7368	2 (3.4)	13 (1.9)	0.4284	0 (0)	1 (4.8)	0.1278
CENP B, n (%)	7 (12.1)	23 (11)	0.8113	7 (5.2)	0 (0)	0.1192	0 (0)	27 (4)	0.1215	9 (18.8)	10 (47.6)	0.0135
AHA, n (%)	1 (1.7)	7 (3.3)	0.5238	2 (1.5)	1 (2.2)	0.7368	13 (22.4)	204 (30.1)	0.2186	5 (10.4)	0 (0)	0.1246
RNP, n (%)	4 (6.9)	12 (5.7)	0.7366	7 (5.2)	2 (4.4)	0.8435	33 (56.9)	254 (37.5)	0.0036	11 (22.9)	4 (19)	0.72
Sm, n (%)	1 (1.7)	3 (1.4)	0.8695	1 (0.7)	0 (0)	0.5626	7 (12.1)	119 (17.6)	0.2874	1 (2.1)	0 (0)	0.5052
Scl-70, n (%)	1 (1.7)	3 (1.4)	0.8695	3 (2.2)	0 (0)	0.3132	2 (3.4)	11 (1.6)	0.311	18 (37.5)	4 (19)	0.1302
Jo-1, n (%)	2 (3.4)	2 (1)	0.1652	10 (7.4)	0 (0)	0.0603	2 (3.4)	4 (0.6)	0.0745	1 (2.1)	0 (0)	0.5052
rRNP, n (%)	2 (3.4)	10 (4.8)	0.6685	3 (2.2)	1 (2.2)	>0.9999	14 (24.1)	176 (26)	0.761	0 (0)	0 (0)	NA

Data are presented as frequency (percentage) for categorical variables and mean ± standard deviation (SD) for continuous variables. *p*-values were calculated using the Chi-squared test or Fisher's exact test for categorical variables and the Mann-Whitney U-test for comparisons of continuous variables between two independent groups.
SjD: Sjögren's disease; IIM: idiopathic inflammatory myopathies; SLE: systemic lupus erythematosus; n: number; SD: standard deviation; ILD: interstitial lung disease; ANA: antinuclear antibody; SSA/Ro60: anti-SSA/Ro60 antibody; Ro 52: anti-Ro52 antibody; dsDNA-CLIA: double-stranded DNA-chemiluminescent immunoassay; PCNA: anti-proliferating cell nuclear antigen antibody; ANuA: anti-nucleosome antibody; SSB: anti-SSB antibody; PM-Scl: anti-PM-Scl antibody; CENP B: anti-centromere protein B antibody; AHA: anti-histone antibody; RNP: anti-ribonucleoprotein antibody; Sm: anti-Sm antibody; Scl-70: anti-Scl-70 antibody; Jo-1: anti-Jo-1 antibody; rRNP: anti-ribosomal RNP antibody.

Table III. ILD progression and mortality across autoimmune diseases.

Disease	Follow-up ILD patients (n)	Progression, n (%)	Non-elective hospitalisation	Absolute FVC decline ≥10%	Lung transplant	All-cause mortality
IIM	88	38 (43.2)	33	7	1	4
SjD	29	14 (48.3)	7	7	0	1
SLE	41	8 (19.5)	5	1	1	2
RA	23	5 (21.7)	3	0	0	2
SSc	28	6 (21.4)	5	2	0	1
AAV	23	13 (56.5)	11	1	0	4
MCTD	12	7 (58.3)	5	2	0	1
OS	36	16 (44.4)	16	1	0	1
Overall AID	280	107 (38.2)	85	21	2	16

Data are presented as frequency (percentage) for categorical variables.
ILD: interstitial lung disease; SjD: Sjögren's disease; IIM: idiopathic inflammatory myopathies; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; SSc: systemic sclerosis; AAV: anti-neutrophil cytoplasmic antibody-associated vasculitis; MCTD: mixed connective tissue disease; OS: overlap syndrome; n: number; FVC: forced vital capacity.

ditionally, Cox regression analysis was performed to evaluate the association between risk factors and ILD progression. ILD progression-free survival was analysed using Kaplan-Meier curves and compared with the log-rank test. Statistical significance was defined as a p-value <0.05. All statistical analyses were performed using R and GraphPad Prism 9.5 (GraphPad Software, LLC, San Diego, CA, USA).

Results

Clinical characteristics of study participants

Our study included 2,021 Chinese patients with AID. Among the AID patients, 268 had SjD, 180 had IIM, 736 had systemic lupus erythematosus (SLE), 145 had RA, 69 had SSc, 116 had anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV), 115 had MCTD, and 60 had overlap syndrome (OS). AID subgroups with fewer than 50 patients were excluded from further analysis.

The mean age of the AID patients was 45.31±17.15 years, and the female-to-male ratio was 3.23 (1,543/478). SLE patients were predominantly young women (36.81±14.81 years, with 87.2% being female). The prevalence of ILD varied across AID subgroups, with the highest rates observed in IIM (75.0%), OS (73.3%), and SSc (69.6%).

The serological profiles of the different AID subgroups, summarised in Table I, revealed distinct differences. ANA positivity was found in 86.1% of SLE patients, 95.7% of SSc patients, and 91.7% of OS patients. Anti-SSA/Ro60 was highly prevalent in SjD (80.6) and in SLE (56.8%). Anti-dsDNA, a hallmark of SLE, were present in 38.7% of SLE patients. Anti-SSB was found in SjD (28.4%) and SLE (10.3%), while anti-Sm were predominantly observed in SLE patients (17.1%). A substantial

proportion of anti-histone (29.5%), anti-RNP (39%), and anti-rRNP (25.8%) was detected in SLE patients. anti-CENP B was notably elevated in SSc (27.5%). anti-Ro52 was observed in 83.6% of SjD patients, 71.7% of IIM patients, and 73.3% of OS patients. It was less frequent in other subgroups, such as AAV and RA.

Clinical and serological characteristics of AID patients with and without ILD

The clinical and serological characteristics of AID patients with and without ILD were compared across various subgroups, as detailed in Table II and Supplementary Table S1. Patients with ILD were significantly older than those without ILD; this age difference was statistically significant in several AID subgroups, except for SSc and OS. Specifically, patients with SjD and ILD were older than those without ILD (59.38±13.32 *vs*. 51.45±15.19 years, p=0.0002). Similar trends were observed in IIM (51.64±13.38 *vs*. 40.4±14.67, p<0.0001), SLE (46±12.96 *vs*. 36.02±14.70, p<0.0001), RA (64.05±9.505 *vs*. 54.57±13.35, p=0.0001) and AAV (62.08±14.25 *vs*. 49.87±19.24, p=0.0003). Gender distribution also varied significantly between ILD and non-ILD patients in AAV, with a higher proportion of males in the ILD group (71.8% *vs*. 39.0%, p=0.0008).

Regarding serological markers, several autoantibodies showed significant associations with the presence of ILD. Anti-Ro52 was significantly more frequent in IIM patients with ILD compared to those without ILD (83.0% *vs*. 37.8%, p<0.0001). Although anti-Ro52 positivity was more common in OS patients with ILD (79.5% *vs*. 56.2%), this difference did not reach statistical significance (p=0.0712). In SLE, anti-RNP was detected at a significantly higher rate in ILD patients (56.9% *vs*. 37.5%, p=0.0036). Interestingly, anti-SSA/Ro60 positivity was significantly lower in SS patients with ILD compared to those without ILD (65.5% *vs*. 84.8%, p=0.001), and a similar trend was observed in the MCTD group (10.3% *vs*. 40.7%, p=0.0027). Additionally, anti-CENP B positivity was significantly reduced in the SSc-ILD group (18.8% *vs*. 47.6%, p=0.0135).

Table IV. Comparison of clinical characteristics and autoantibody profiles between progressors and non-progressors in AID-ILD.

	No progression (n=173)	Progression (n=107)	*p*-value
Age, mean ± SD	51.35 ± 14.56	53.05 ± 16.23	0.2084
Disease duration, mean ± SD	4.80 ± 6.78	4.18 ± 6.46	0.4032
Female, n (%)	136 (78.6%)	80 (74.8%)	0.5496
Smoking, n (%)	17 (9.8%)	9 (8.4%)	0.8535
Glucocorticoids, n (%)	115 (66.5%)	61 (57.0%)	0.1428
Immunosuppressant, n (%)	103 (59.5%)	48 (44.9%)	0.0232
NSIP, n (%)	86 (49.7%)	55 (51.4%)	0.7833
UIP, n (%)	83 (48.0%)	48 (44.9%)	0.2629
OP, n (%)	4 (2.3%)	4 (3.7%)	0.4862
SSA/Ro60, n (%)	62 (35.8%)	43 (40.2%)	0.5463
Ro 52, n (%)	107 (61.8%)	72 (67.3%)	0.4278
ANA, n (%)	130 (75.1%)	70 (65.4%)	0.1065
dsDNA-CLIA, n (%)	21 (12.1%)	6 (5.6%)	0.1117
PCNA, n (%)	3 (1.7%)	0 (0.0%)	0.44
ANuA, n (%)	13 (7.5%)	4 (3.7%)	0.3039
SSB, n (%)	10 (5.8%)	15 (14.0%)	0.0329
PM-Scl, n (%)	6 (3.5%)	1 (0.9%)	0.3546
CENP B, n (%)	13 (7.5%)	7 (6.5%)	0.9456
AHA, n (%)	16 (9.2%)	8 (7.5%)	0.768
RNP, n (%)	41 (23.7%)	18 (16.8%)	0.2223
Sm, n (%)	8 (4.6%)	2 (1.9%)	0.3812
Scl-70, n (%)	14 (8.1%)	5 (4.7%)	0.3892
Jo-1, n (%)	10 (5.8%)	5 (4.7%)	0.8991
rRNP, n (%)	12 (6.9%)	6 (5.6%)	0.8494

Data are presented as frequency (percentage) for categorical variables and mean ± standard deviation (SD) for continuous variables.
p-values were calculated using the Chi-squared test or Fisher's exact test for categorical variables and the Mann-Whitney U-test for comparisons of continuous variables between two independent groups.
ANA: antinuclear antibody; SSA/Ro60: anti-SSA/Ro60 antibody; Ro 52: anti-Ro52 antibody; dsDNA-CLIA: double-stranded DNA-chemiluminescent immunoassay; PCNA: anti-proliferating cell nuclear antigen antibody; ANuA: anti-nucleosome antibody; SSB: anti-SSB antibody; PM-Scl: anti-PM-Scl antibody; CENP B: anti-centromere protein B antibody; AHA: anti-histone antibody; RNP: anti-ribonucleoprotein antibody; Sm: anti-Sm antibody; Scl-70: Anti-Scl-70 antibody; Jo-1: anti-Jo-1 antibody; rRNP: anti-ribosomal RNP antibody; NSIP: non-specific interstitial pneumonia; UIP: usual interstitial pneumonia; OP: organising pneumonia.

Table V. Disease-specific Cox analysis for anti-Ro52 and ILD progression.

Disease subtype	Follow-up ILD patients (n)	Anti-Ro52 positive, n (%)	HR (95% CI)	*p*-value
IIM	88	73 (83.0)	1.0959 (0.5597–2.1459)	0.9938
SjD	29	24 (82.8)	0.7639 (0.3306–1.7650)	0.3141
SLE	41	29 (70.7)	2.8966 (0.3982–21.0712)	0.2677
RA	23	4 (17.4)	1.1875 (0.1762–8.0011)	0.9363
SSc	28	15 (53.6)	1.7333 (0.3767–7.9753)	0.4197
AAV	23	3 (13.0)	1.2121 (0.4963–2.9605)	0.8432
MCTD	12	3 (25.0)	2.2500 (1.0838–4.6710)	0.0034
OS	36	28 (77.8)	0.8571 (0.3797–1.9351)	0.5789
Overall AID	280	179 (63.9)	1.1607 (0.8413–1.6015)	0.5332

Data are presented as frequency (percentage) for categorical variables. Cox regression analysis was performed to evaluate the association between risk factors and ILD progression.
ILD: interstitial lung disease; SjD: Sjögren's disease; IIM: idiopathic inflammatory myopathies; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; SSc: systemic sclerosis; AAV: anti-neutrophil cytoplasmic antibody-associated vasculitis; MCTD: mixed connective tissue disease; OS: overlap syndrome; n: number; HR: hazard ratio; CI: confidence interval.

ILD progression across AID subtypes and anti-Ro52 association

Among 280 patients with AID-ILD, ILD progression occurred in 107 patients (38.2%) during follow-up (Table III). Progression rates varied significantly across AID subtypes, being highest in MCTD (58.3%), AAV (56.5%), and SjD (48.3%), and lowest in SLE (19.5%), RA (21.7%), and SSc (21.4%). During follow-up, 85 non-elective hospitalisations, 21 instances of absolute FVC decline ≥10%, 2 lung transplants, and 16

Table VI. Positivity rates for myositis-specific autoantibodies and interstitial lung disease across all IIM patients and subtypes.

Variable	Total IIM	Dermatomyositis	Polymyositis	Overlap myositis	Anti-synthetase syndrome	Amyopathic dermatomyositis	Immune-mediated necrotising myopathy	Paraneoplastic dermatomyositis
n	180	85	17	24	32	9	9	4
ILD (+)	135 (75.0)	64 (75.3)	6 (35.3)	19 (79.2)	32 (100.0)	9 (100.0)	3 (33.3)	2 (50.0)
Ro52, n (%)	129 (71.7)	58 (68.2)	7 (41.2)	20 (83.3)	28 (87.5)	8 (88.9)	7 (77.8)	1 (25.0)
MDA5, n (%)	55 (30.6)	47 (55.3)	0 (0.0)	2 (8.3)	0 (0.0)	5 (55.6)	0 (0.0)	1 (25.0)
OJ, n (%)	7 (3.9)	1 (1.2)	0 (0.0)	1 (4.2)	5 (15.6)	0 (0.0)	0 (0.0)	0 (0.0)
EJ, n (%)	14 (7.8)	1 (1.2)	0 (0.0)	3 (12.5)	8 (25.0)	1 (11.1)	1 (11.1)	0 (0.0)
PL-12, n (%)	9 (5.0)	2 (2.4)	0 (0.0)	1 (4.2)	6 (18.8)	0 (0.0)	0 (0.0)	0 (0.0)
PL-7, n (%)	17 (9.4)	4 (4.7)	1 (5.9)	1 (4.2)	10 (31.3)	1 (11.1)	0 (0.0)	0 (0.0)
Jo-1, n (%)	10 (5.6)	0 (0.0)	1 (5.9)	3 (12.5)	6 (18.8)	0 (0.0)	0 (0.0)	0 (0.0)
SRP, n (%)	14 (7.8)	2 (2.4)	2 (11.8)	4 (16.7)	1 (3.1)	1 (11.1)	4 (44.4)	0 (0.0)
PM75, n (%)	11 (6.1)	3 (3.5)	0 (0.0)	3 (12.5)	4 (12.5)	0 (0.0)	1 (11.1)	0 (0.0)
PM100, n (%)	6 (3.3)	4 (4.7)	0 (0.0)	2 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ku, n (%)	3 (1.7)	0 (0.0)	0 (0.0)	1 (4.2)	1 (3.1)	0 (0.0)	1 (11.1)	0 (0.0)
SAE1, n (%)	3 (1.7)	1 (1.2)	0 (0.0)	0 (0.0)	1 (3.1)	1 (11.1)	0 (0.0)	0 (0.0)
NXP2, n (%)	10 (5.6)	9 (10.6)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TIF1g, n (%)	14 (7.8)	8 (9.4)	1 (5.9)	2 (8.3)	0 (0.0)	1 (11.1)	0 (0.0)	2 (50.0)
Mi-2b, n (%)	6 (3.3)	4 (4.7)	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	1 (25.0)
Mi-2a, n (%)	3 (1.7)	2 (2.4)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Data are presented as frequency (percentage).
n: number; ILD: interstitial lung disease; Ro52: anti-Ro52 antibody; MDA5: anti-MDA5 Antibody; OJ: anti-OJ antibody; EJ: anti-EJ antibody; PL-12: anti-PL-12 antibody; PL-7: anti-PL-7 antibody; Jo-1: anti-Jo-1 antibody; SRP: anti-signal recognition particle antibody; PM75: anti-PM75 antibody; PM100: anti-PM100 antibody; Ku: anti-Ku antibody; SAE1: anti-SAE1 antibody; NXP2: anti-NXP2 antibody; TIF1g: anti-TIF1γ antibody; Mi-2b: anti-Mi-2b antibody; Mi-2a: anti-Mi-2a antibody.

Table VII. Lasso analysis of myositis-specific autoantibodies and predictors for ILD in IIM patients.

Variable	LASSO coefficient	LASSO odds ratio	LASSO importance	Rank	Odds ratio (final model)	CI lower	CI upper	*p*-value
MDA5	0.787	2.196	0.787	1	5.898	2.097	16.59	0.00077
age	0.594	1.811	0.594	2	2.842	1.76	4.587	1.91E-05
Ro52	0.588	1.801	0.588	3	2.508	1.664	3.778	1.11E-05
TIF1g	-0.13	0.878	0.13	4				
PL-7	0.102	1.107	0.102	5				
Jo-1	0.101	1.106	0.101	6				
EJ	0.042	1.043	0.042	7				
OJ	0.037	1.037	0.037	8				
PL-12	0	1	0	9				
SRP	0	1	0	10				
PM75	0	1	0	11				
PM100	0	1	0	12				
Ku	0	1	0	13				
SAE1	0	1	0	14				
NXP2	0	1	0	15				
Mi-2b	0	1	0	16				
Mi-2a	0	1	0	17				
gender	0	1	0	18				

IIM: idiopathic inflammatory myopathies; ILD: interstitial lung disease; MDA5: anti-MDA5 antibody; Ro52: anti-Ro52 antibody; TIF1γ: anti-TIF1γ antibody; PL-7: anti-PL-7 antibody; Jo-1: anti-Jo-1 antibody; EJ: anti-EJ antibody; OJ: anti-OJ antibody; PL-12: anti-PL-12 antibody; SRP: anti-signal recognition particle antibody; PM75: anti-PM75 antibody; PM100: anti-PM100 antibody; Ku: anti-Ku antibody; SAE1: anti-SAE1 antibody; NXP2: anti-NXP2 antibody; Mi-2b: anti-Mi-2b antibody; Mi-2a: anti-Mi-2a antibody; CI: confidence interval.

deaths were recorded, with the highest event burdens observed in IIM and AAV. Clinical characteristics and autoantibody profiles were compared between patients with progressive and non-progressive AID-ILD (Table IV). Regarding treatment exposure, immunosuppressant use was less frequent in progressors than in non-progressors (44.9% *vs*. 59.5%, *p*=0.023). Most autoantibodies showed similar prevalences between the two groups. However, anti-SSB antibodies were more commonly detected in progressors than in non-progressors (14.0% *vs*. 5.8%, *p*=0.033).

Cox proportional hazards analysis revealed no significant association between anti-Ro52 positivity and ILD progression in the overall cohort (HR 1.16, 95% CI 0.84–1.60; *p*=0.53) (Table V). However, disease-specific analysis identified a significant association in MCTD, where anti-Ro52 positivity was associated with more than a twofold increased risk of ILD progression (HR 2.25, 95% CI 1.08–4.67; *p*=0.003). No significant associations were found in other AID subtypes.

After analysing the association between anti-Ro52 and ILD progression, we

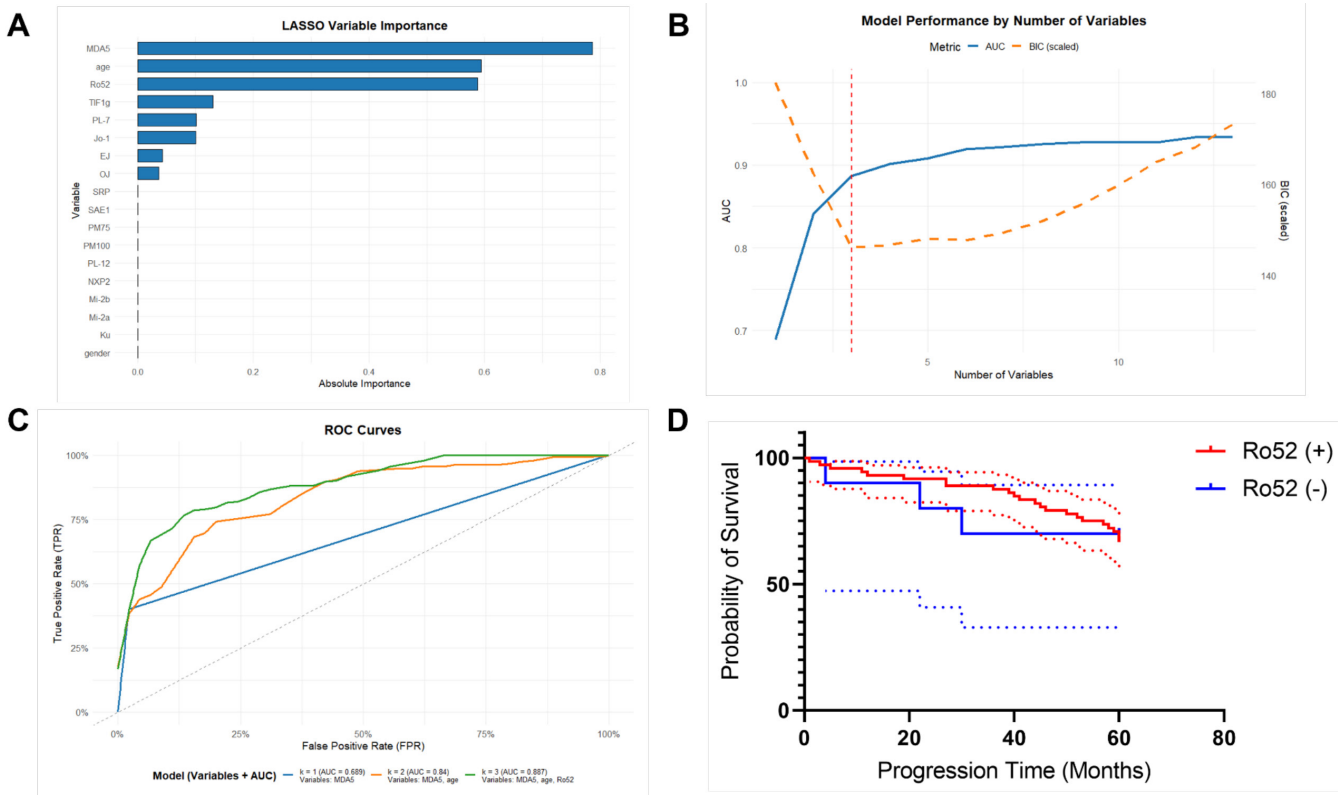

Fig. 1. Association of anti-Ro52 positivity with ILD in IIM patients.
A: Variable importance derived from LASSO regression, measured by the absolute value of regression coefficients.
B: Model performance metrics across different numbers of selected variables. The blue solid line represents the area under the ROC curve (AUC), the orange dashed line shows the scaled Bayesian Information Criterion (BIC), the vertical red dashed line marks the optimal number of variables selected based on the minimum BIC.
C: Receiver operating characteristic (ROC) curves for models with 1, 2, and 3 predictors derived from LASSO analysis.
D: Kaplan-Meier curves for the ILD progression-free survival with or without anti-Ro52 antibodies. The log-rank test was used to compare the groups.

further investigated anti-Ro60, another Ro/SSA family autoantibody relevant to autoimmune lung involvement. As shown in Supplementary Table S2, anti-Ro60 positivity was not significantly associated with ILD progression in any subtype or the overall cohort.

Association of anti-Ro52 and anti-MDA5 with ILD occurrence and progression in IIM patients

Building upon our previous findings that anti-Ro52 positivity is associated with ILD in IIM patients, we further analysed the significance of anti-Ro52, myositis-specific antibodies (MSAs) and myositis-associated antibodies (MAAs) in this cohort. Table VI summarises the positivity rates for MSAs, MAAs and ILD across all IIM patients and its subtypes. Among the 180 total patients with IIM, 135 (75%) had ILD. The highest prevalence was observed in anti-synthetase syndrome (100%, n=32/32) and amyopathic dermatomyositis (ADM; 100%, n=9/9).

To evaluate the predictive importance of anti-Ro52, MSAs, MAAs and demographic factors (age, gender) for ILD, we performed LASSO regression analysis. Table VII and Figure 1A present the LASSO importance scores, with anti-MDA5 (coefficient = 0.787) being the most significant predictor. Other notable variables included age (coefficient = 0.594) and anti-Ro52 (coefficient = 0.588). Using the Bayesian Information Criterion (BIC), we identified the optimal set of three variables (anti-MDA5, age, and anti-Ro52) for the final model, which was based on the lowest BIC value (Fig. 1B). AUC and BIC for various variable combinations are shown in Supplementary Table S3. In the final model, anti-MDA5 demonstrated an odds ratio of 5.898 (95% CI: 2.097 to 16.59, p=0.00077), indicating a strong association with ILD. Age also emerged as a significant predictor, with an odds ratio of 2.842 (95% CI: 1.76 to 4.587, p=1.91E-05), suggesting that older patients are at higher risk for ILD. Anti-Ro52 was another important predictor, with an odds ratio of 2.508 (95% CI: 1.664 to 3.778, p=1.11E-05) (Table VII). The final model, including anti-MDA5, age, and anti-Ro52, showed an AUC of 0.887 (Fig. 1C) and a BIC of 146.01 (Suppl. Table S3).

Finally, we examined the predictive ability of anti-Ro52 positivity for ILD progression in IIM-ILD patients. A total of 88 IIM-ILD patients with follow-up data were included in the Kaplan-Meier analysis for ILD progression-free survival, stratified by the presence of anti-Ro52 (Fig. 1D). No significant difference was found between the groups, as indicated by a log-rank test (p=0.9761) and a hazard ratio of 1.018 (95% CI: 0.3093 to 3.354).

Discussion

In this study, we investigated the association between various autoantibodies and ILD in patients with AID.

The prevalence of ILD varied across AID subgroups, with the highest rates observed in IIM (75.0%). Additionally, distinct autoantibody profiles were identified among the different AID subgroups. Anti-Ro52 was found in 83.6% of SjD patients, 71.7% of IIM patients, and 73.3% of OS patients. Further comparison between AID patients with and without ILD revealed that anti-Ro52 was significantly more prevalent in IIM patients with ILD than in those without ILD. LASSO regression analysis identified anti-Ro52, age, and anti-MDA5 as significant predictors of ILD development in IIM, suggesting that anti-Ro52 may play an independent role in the presence of ILD among these patients.

Anti-Ro52 (also known as anti-TRIM21) is a member of the anti-Ro/SSA antibody family, traditionally considered a marker for SjD and SLE (10). Its specificity in CTD is limited, yet growing evidence links isolated anti-Ro52 positivity to various CTD (11, 12). In 2012, Ferreira *et al*. first demonstrated that anti-Ro52 antibodies were significantly associated with ILD in CTD patients, identifying them as highly sensitive markers for ILD diagnosis (13). Subsequent research confirmed its association with ILD occurrence, severity, and progression in SjD, ASS, and DM (14-18). In line with these findings, *Sabbagh et al*. reported that anti-Ro52 was independently associated with both the frequency and severity of juvenile myositis-related ILD and the presence of Raynaud's phenomenon (19). Consistently, our findings show that anti-Ro52 positivity in IIM patients increases the risk of developing ILD approximately 2.5-fold.

The mechanisms by which anti-Ro52 contribute to ILD remain incompletely understood, but evidence suggests a key role in immune regulation and inflammation (7, 10). Ro52, an E3 ubiquitin ligase, ubiquitinates proteins including interferon regulatory factors, which activate type I interferons (IFNs) and pro-inflammatory cytokines (20). Type I IFNs promote CX3CL secretion, recruiting $CX3CR1^{+}$ M2 macrophages to the lungs, where they release TGF-β, a driver of fibrosis(21). These cytokines are closely associated with fibrosis pathways and are known to contribute to poor prognosis in ILD (22, 23). Ro52 is itself induced by type I IFNs, forming a feedback loop that limits excessive immune responses (7). Anti-Ro52 may disrupt this regulation, as immune complexes containing anti-Ro52 can enhance IFNα production, promoting uncontrolled inflammation (24). High Ro52 expression in lung tissue further predisposes to immune dysregulation, contributing to ILD development. Thus, anti-Ro52 may act not only as a biomarker but also as an active participant in ILD pathogenesis.

We evaluated the predictive value of anti-Ro52 positivity for ILD progression in IIM-ILD patients. A Kaplan-Meier analysis of 82 patients with follow-up data showed no significant difference in ILD progression-free survival based on anti-Ro52 status. This lack of association may be due to the small sample size, highlighting the need for validation in larger cohorts. Similarly, another study found that although univariate analysis suggested anti-Ro52 as a predictor for ILD progression in IIM patients, it was not an independent risk factor after multivariate analysis (25). Another study reported no differences in mortality (both overall and disease-related) between anti-Ro52-positive and negative patients, despite a higher incidence of ILD in the anti-Ro52-positive group. Survival curves did not differ at any time point (26). In contrast, a study found that patients with isolated anti-Ro52-associated RP-ILD had the highest survival rates compared to those with other myositis-specific autoantibodies, although the difference was not statistically significant (27). Furthermore, multivariate Cox regression analysis identified anti-Ro52 positivity as an independent risk factor for RP-ILD, but not for mortality, in anti-MDA5-positive DM patients (28). Despite these mixed findings, a substantial body of literature suggests a strong association between anti-Ro52 and ILD development and progression. Studies have shown that anti-Ro52-positive myopathy patients are more likely to develop RP-ILD (6). In juvenile dermatomyositis, anti-Ro52 positivity correlates with a more severe/chronic disease course, less frequent remission and increased medication use (19). Additionally, in antisynthetase syndrome, anti-Ro52-positive patients often exhibit ILD with a poorer prognosis (15). Ghillani *et al*. highlighted the potential of anti-Ro52 as an early marker for AID-related ILD progression, while other studies suggest that anti-Ro52, along with high titers of anti-U1 RNP, may serve as predictors of lung fibrosis and ILD progression in MCTD (29-31). In conclusion, while there is evidence suggesting an association between anti-Ro52 and ILD progression in IIM patients, its role as a reliable prognostic marker remains controversial and warrants further investigation.

Earlier studies have shown that anti-MDA5 positivity in IIM is associated with a higher risk of ILD compared to patients with negative antibodies or those with other myositis-specific antibodies (32-37). In a study by Wen *et al*., anti-MDA5 was the most common myositis-specific antibody in IIM patients and was significantly linked to rapidly progressive ILD. Patients with both anti-MDA5 and anti-Ro52 had the worst prognosis (38). Consistent findings from multiple studies have demonstrated that anti-Ro52 increase the risk of rapidly progressive ILD and are associated with lower survival rates in patients with anti-MDA5 positive DM and IIM-associated ILD, with particularly poor outcomes in those who are positive for both anti-MDA5 and anti-Ro52 (28, 39, 40, 41). In our study, we observed an increased risk of ILD in patients with either anti-MDA5 or anti-Ro52 positivity, and after adjusting for anti-MDA5 positivity, the association with anti-Ro52 remained significant, suggesting that anti-Ro52 may play an independent role in the presence of ILD in these patients. Notably, these observations are derived from a cohort consisting exclusively of Chinese patients and are consistent with reports from other Asian populations, whereas the prevalence and prognostic impact of anti-MDA5 and anti-Ro52 may differ in Western cohorts, highlighting the potential influence of ethnic and genetic background on disease expression.

In our study, anti-RNP antibodies were detected at a significantly higher rate

in SLE patients with ILD compared to those without ILD (56.9% *vs*. 37.5%, p=0.0036). The presence of anti-U1-RNP antibodies in patients meeting SLE classification criteria has been associated with pulmonary involvement and impaired lung function (42, 43). Seropositivity for anti-RNP has also been linked to shrinking lung syndrome when compared with symptomatic controls (44) and, more broadly, to reduced pulmonary function and other pulmonary manifestations, as confirmed by meta-analyses (45). Furthermore, higher anti-RNP antibody levels have been reported in patients with lupus nephritis, and delayed onset of nephritis has been positively associated with lung involvement (46). Notably, anti-survival motor neuron (SMN) complex antibodies, which often coexist with anti-U1-RNP antibodies, have been identified as biomarkers of a subset of MCTD patients who frequently develop ILD (47). Importantly, our study provides the first direct evidence of a specific association between anti-RNP antibodies and ILD in SLE, distinguishing it from previous reports that largely focused on broader pulmonary involvement or on MCTD cohorts. These findings suggest that anti-RNP seropositivity may serve as a potential biomarker for risk stratification of pulmonary involvement in SLE, highlighting its clinical relevance for early identification and monitoring of patients at higher risk of ILD.

Interestingly, we found that the frequency of anti-SSA/Ro60 was lower in SjD -ILD patients compared to those without ILD. This finding aligns with a previous study showing that anti-SSA and anti-SSB negativity was positively associated with ILD in patients with Sjögren's Disease (48). Additionally, SSc patients with ILD had a higher prevalence of anti-Ro52 (p=0.046), but a lower prevalence of anti-CENP B (p<0.001) (49). This inverse relationship between anti-CENP B positivity and ILD presence has also been reported in other studies, which found that SSc-ILD was less frequent in patients with anti-CENP B (p<0.001) (50, 51). These findings are consistent with our results.

This study has several limitations. Firstly, its retrospective, single-centre design introduces the potential for selection bias and limits the generalisability of findings to the broader AID population. This may affect the detection of significant associations, particularly in smaller IIM subgroups. Future prospective, multicentre and longitudinal studies with larger cohorts are needed to confirm the role of anti-Ro52 as a predictive biomarker for ILD. Secondly, the study was limited by missing clinical and serological data for some patients, which may impact the results. Third, the inclusion of hospitalised patients only may have introduced selection bias toward individuals with higher disease activity or greater diagnostic complexity. Consequently, the findings are likely most applicable to patients with more severe or hospitalised AID-ILD and may not be fully generalisable to milder cases managed in outpatient settings. Lastly, while regression analyses identified potential risk factors, these associations do not establish causation. Further mechanistic studies are needed to clarify the underlying mechanisms.

In conclusion, this study highlights anti-Ro52 as a promising biomarker for ILD in DM patients and provides a foundation for future research aimed at improving early detection and personalised treatment strategies for these high-risk individuals.

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