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Clinical science

Antibody predictors of mortality and lung function trends in myositis spectrum interstitial lung disease

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Abstract

Objectives: The impact of autoantibody profiles on the prognosis for idiopathic inflammatory myositis–associated interstitial lung disease (IIM-ILD) and myositis spectrum ILD with myositis-specific antibodies (MSAs) remains unclear. This retrospective cohort study examined whether serological profiles were associated with mortality or longitudinal lung function change.

Methods: The baseline clinical/demographic characteristics and follow-up lung function data of consecutive adult patients with IIM-ILD or interstitial pneumonia with autoimmune features (IPAF) positive for MSAs (IPAF-MSA) were extracted from three hospitals. Univariate and multivariate Cox proportional hazards analyses were used to compare mortality between groups of patients with different autoantibodies. Regression models were used to analyse their lung function trends.

Results: Of the 430 included patients, 81% met the IIM criteria, and the remaining 19% were diagnosed with IPAF-MSA. On univariate analysis, the risk factors associated with mortality included higher age, Charlson Comorbidity Index, and CRP; and lower BMI, baseline TLCO% and FEV1%. Compared with anti-MDA5 negativity, anti-MDA5 positivity (MDA5+) was associated with higher mortality in the first 3 months [hazard ratio (HR) 65.2, 95% CI 14.1, 302.0], while no significant difference was seen thereafter (HR 0.55, 95% CI 0.14, 2.28). On multivariate analysis, combined anti-synthetase antibodies were associated with a reduced risk of mortality (HR 0.63), although individually, mortality was reduced in patients with anti-Jo1+ (HR 0.61, 95% CI 0.4–0.87) and increased in patients with anti-PL7+ (HR 2.07, 95% CI 1.44–2.99). Anti-MDA5+ was associated with slow improvement in %FVC over the first 3 years, while anti-PL7+ was linked with a slow decline from 12 months onwards.

Conclusion: Among the autoantibody profiles in myositis spectrum disorders, anti-MDA5+ and anti-PL7+ conferred higher mortality risks in patients with IIM-ILD. Survivors of an early peak of mortality in anti-MDA5+ disease appeared to have a favourable prognosis.

Keywords: myositis, idiopathic inflammatory myopathies, interstitial lung disease, autoantibodies, mortality, progression.

Rheumatology key messages

- Anti-MDA5 was associated with increased early mortality in the largest European cohort of patients with studied to date.
- Survivors of early anti-MDA5+ IIM-ILD had a favourable prognosis in terms of both lung function progression and mortality.
- The prognosis differed between patients with different anti-synthetases. Positivity for anti-PL7+ was a risk factor for mortality. Positivity for anti-Jo1+ was associated with improved survival.

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Introduction

The idiopathic inflammatory myopathies (IIMs) are a spectrum of rare, multisystem, auto-immune conditions most commonly affecting the muscles, skin, heart and/or lungs. Interstitial lung disease (ILD) is a frequent and feared complication of IIM, affecting ∼40% of patients [1]. It is associated with increased morbidity, and is one of the strongest predictors of mortality in IIM [2, 3].

Presentation of IIM-associated ILD (IIM-ILD) can range from asymptomatic to acute fulminant respiratory failure. The clinical course can be unpredictable. Differentiating those patients likely to progress despite treatment, from those who will display major improvements with immunomodulatory therapy or remain indolent, is not straightforward. Many studies have attempted to identify risk factors, although obtaining conclusive findings is hindered by small populations and the heterogeneity of underlying conditions.

Myositis-specific antibodies (MSAs) and myositis-associated antibodies (MAAs) are commonly detected in the sera of IIM patients. MSAs include antibodies against Jo1, PL7, PL12, EJ, OJ, Mi2, SRP, NXP2, TIF1G and MDA5, and are quite specific to IIM. MAAs are frequently seen in alternative or overlap CTDs as well as in IIM, and include antibodies against RNP, Ro52, Ku and PM/Scl. It is well established that MSA and MAA patterns are associated with different IIM disease phenotypes, with certain antibodies being more commonly associated with the development of ILD: specifically, Jo1, PL7, PL12, Ro52 and MDA5 antibodies confer increased risk of ILD, whereas anti-NXP2, anti-Tif1g and anti-Mi2 are associated with lower ILD prevalence [4]. Anti-MDA5+ patients make up a small proportion of IIMs but are heavily studied due to a suggested association with rapidly progressive ILD and early mortality [5]. However, almost all research in this area is from East Asia, so there may be genetic or environmental factors that reduce generalizability to other populations. Studies in East Asia show a much higher prevalence of anti-MDA5+ disease than in European or North American cohorts [6]. A meta-analysis had observed anti-tRNA-synthetases (ARS) to be associated with comparatively lower mortality, but heterogeneity in the cohort was high, and clinical phenotypes may vary between ARS antibodies [5].

This study aimed to assess a multicentre UK cohort to establish whether MSAs or MAAs can be used to predict outcomes in IIM-ILD.

Methods

This retrospective cohort used the electronic medical records of patients with IIM-ILD across three National Health Service hospital trusts in London, UK: King's College Hospitals, Royal Brompton and Harefield Hospitals and Guy's and St Thomas' Hospitals. A broad search for consecutive patients seen between 2011 and 2021 in rheumatology or ILD specialist services was conducted using outpatient clinical databases and immunology laboratory reports. Electronic records were reviewed for probable diagnosis of IIM according to EULAR/ACR 2017, Bohan & Peter's, or Connors' anti-synthetase criteria [7–9]. Patients were also included if they met ERS/ATS criteria for interstitial pneumonia with autoimmune features (IPAFs) and had a positive MSA (IPAF-MSA) [10]. IPAF patients were excluded if they were only positive for an MAA, or if the MSA was only weakly positive (<10 units), due to low positive predictive value at low titres [11]. ILD was confirmed by CT radiography and multidisciplinary team assessment. Patients with overlap CTDs (ie. those who also met the criteria for an alternative defined CTD) were not excluded as long as they also met the EULAR/ACR 2017 IIM diagnostic criteria. Patients were excluded if they had an alternative ILD diagnosis (e.g. idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, obliterative bronchiolitis), or if an MSA result was unavailable. All antibody tests were performed on EUROLINE immunoblot (Euroimmun, Busy-Saint-Martin, France) or by immunoprecipitation.

Baseline demographic, clinical, immunological, and radiographic characteristics were recorded from the time of the first inpatient/outpatient hospital presentation with symptoms/signs of ILD. Immunosuppressive medications given in the first 6 months were recorded. The primary end point was all-cause mortality. For patients with lung function measured on more than one occasion, a secondary, composite end point for progression-free survival was composed of Forced Vital Capacity (FVC) ± Transfer Factor for Cabon Monoxide (TLCO) deterioration, lung transplantation, or death. Lung function deterioration was defined as ≥10% reduction in FVC or ≥15% reduction in TLCO accompanied by ≥5 to <10% reduction in FVC according to the OMERACT criteria, without subsequent recovery [12].

The date of death was taken from electronic health records linked to National Health Service Personal Demographics Service, such that all deceased cases were accurately identified. The exit date in the surviving patients was taken as the date of the most recent hospital visit. Data collection took place between June 2021 and December 2022. For the secondary end point of progression-free survival, the start time was taken as the date of the first lung function test, and censoring occurred at the time of the last lung function test, at death, or at transplant, which were considered surrogate indicators of end-stage lung disease.

Possible pulmonary arterial hypertension (PAH) was pragmatically defined as echocardiogram-estimated pulmonary artery systolic pressure (PASP) of >30 mHg within the first year of presentation, unless subsequently disproved by right heart catheterization. Though elevated PASP is not diagnostic of PAH, PASP of >30 mmHg has been independently linked to increased mortality [13, 14].

Statistical methods

All statistical modelling was performed using Stata-17 [15]. Differences in the baseline characteristics between antibody groups were tested using χ^2 for categorical variables, and Kruskal–Wallis groups for continuous variables. Missing data was handled by multiple imputation by chained equation (MICE) modelling with 40 iterations [16]. Survival analysis using Cox proportional hazards was performed to compare time to all-cause mortality according to the baseline characteristics and the presence of individual autoantibodies (compared against all others combined). Multivariate models were created for antibody status, adjusting for confounders identified using a direct acyclic graph chart [17]. Clustering within a hospital was accounted for using the robust sandwich estimator. Sensitivity analysis was performed with a maximally adjusted model, including additional baseline variables identified as significant on univariate analysis.

Exploratory multilevel mixed-effect models for repeated measures over time using a 4-knot spline were used to observe

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trends in lung function according to antibody. Transplanted patients were censored at the time of lung transplant.

Post-hoc joint modelling, in which a linear mixed-effects submodel and a survival submodel are simultaneously estimated, was performed to probe for an effect of survivor bias on lung function trends over time in anti-MDA5+ disease using the *stjm* command in Stata.

Significance was evaluated at an alpha threshold of 0.05 using a two-sided hypothesis test for the primary outcome. For other analyses, nominal *P* values are presented, but the findings should be considered to be hypothesis generating, rather than confirmatory, as no correction for multiplicity is being made.

Ethical approval was granted via IRAS (286985). Ethical permission was granted to collect anonymized data without individualized consent, as only previously collected data were being used, and non-anonymized health-care records were only being accessed by clinician researchers from within each patient's own care team.

Results

Baseline characteristics

A total of 10 800 records were screened, and 430 eligible patients with IIM-ILD were identified (Supplementary Fig. S1, available at *Rheumatology* online). MSAs were present in 275/430 (64.0%) patients and MAAs seen in 255/430 (59.3%). Only 9 of the MSA-positive patients (3%) had co-existing MSAs, confirming that MSAs were largely mutually exclusive.

Of the 430 eligible patients, 67.7% were female and the mean age was 52.6 years (95% CI 51.3, 53.9); 45.6% were Caucasian, 39.1% were non-Caucasian and 15.4% were of unknown ethnicity. IIM/anti-synthetase syndrome (ASS) classification criteria were met by 80.9% of patients, with the remaining being diagnosed with IPAF-MSA. Despite MAAs occurring in nearly 60% of the eligible patients, clinical overlap with other CTDs had been diagnosed in only 49 (11.4%), consisting of unspecified/mixed CTD ($n = 17$), SSc ($n = 11$), RA ($n = 8$), SS ($n = 7$) and SLE ($n = 6$). Possible PAH (PASP of >30 mmHg) was found in 9.8% of the eligible patients within 1 year of diagnosis. Only 3.7% had an identified malignancy within 3 years of ILD diagnosis. MMF was the most commonly prescribed immunomodulatory drug in the first 6 months (39%), and 33% were given either rituximab or CYC, 17% received AZA, 9% received HCQ, 6% received calcineurin inhibitors, and 6% received MTX.

Table 1 compares the baseline characteristics across broad antibody groups. Significant differences were observed between antibody subgroups in age, BMI, frequency of IPAF-MSA, baseline creatine kinase, baseline %predicted Carbon Monoxide Transfer Coefficient (KCO), early treatment with rituximab or CYC, PASP of >30 mmHg, presence of overlap CTD features, acute presentation requiring hospitalization within the first month, and follow-up duration.

Primary end point

Univariate Cox modelling showed that increased age, Charlson Comorbidity Index and CRP, and lower BMI, baseline TLCO% and Forced Expiratory Volume in first 1 second (FEV1)% were associated with increased all-cause mortality (Table 2). Also associated with increased mortality was PASP of >30 mmHg, smoking history, and hospitalization within the first month (i.e. acute presentation). All remained significant on multivariate analysis except BMI and acute presentation.

In patients with anti-MDA-5+, most deaths occurred early, as shown by the Kaplan–Meier curve (Fig. 1), thereby violating the assumption of proportionality. Anti-MDA-5+ survival analysis was therefore performed separately to other groups by splitting the cohort at 3 months. The risk of 3-month mortality was increased in patients with anti-MDA5+ (HR 65.2, 95% CI 14.1, 302.0), whereas mortality after this point was non-significantly lower than that for MDA5-negative patients (HR 0.55, 95% CI 0.14, 2.28). Increased mortality in the first 3 months remained significant on multivariate modelling after adjusting for age, sex, ethnicity, malignancy, overlap CTD status, and hospital site ($P = 0.02$). Risk of mortality among the MDA-5 positive individuals was increased in males (HR 5.32, 95% CI 1.24, 22.88), patients with acute presentation (HR 12.1, 95% CI 1.36, 107.85), and patients with increased CRP (HR 1.02, 95% CI 1.01, 1.03).

Anti-PL7+ antibodies were associated with increased mortality on univariate analysis (HR 2.29, 95% CI 1.22, 4.31), whereas anti-Jo1+ antibodies were associated with improved survival (HR 0.56, 95% CI 0.35, 0.91) (Fig. 2, Table 3). These associations remained significant after adjusting for age, sex, ethnicity, malignancy, overlap CTD status, and hospital site (Table 3). Additionally, this multivariate model demonstrated increased mortality in the anti-RNP+ group (HR 1.90, 95% CI 1.24, 2.93). Despite the association between anti-PL7+ and mortality, the anti-synthetase group as a whole was associated with improved survival, both on univariable and multivariable analysis (adjusted HR 0.64, 95% CI 0.52, 0.77) (Table 3). Sensitivity analysis with additional adjustment for other significant baseline variables, including baseline TLCO, FVC and FEV1, BMI, estimated PASP of >30 mmHg and CRP, did not change the significance of any of the above results (data not shown). The presence of anti-Ro52 was not associated with mortality. Fifty-five patients had both anti-Jo1 and anti-Ro52 antibodies. Among those positive for anti-Jo1, the presence of anti-Ro52 did not significantly increase mortality (HR 1.50, 95% CI 0.74, 3.04). Thirteen patients were positive for both anti-MDA5 and anti-Ro52. Survival also did not differ significantly within this subgroup between those who were anti-Ro52 positive and those who were negative (adjusted HR 1.76, 95% CI 0.34, 9.11).

Secondary end point

Of the subjects, 338 had sufficient lung function data available to contribute to secondary end point analysis. Anti-Ku+ was associated with reduced progression-free survival on univariate analysis, (HR 2.98, 95% CI 1.29, 6.87) (Table 3 and Supplementary Fig. S2, available at *Rheumatology* online); however, this was no longer significant on multivariate modelling. In contrast, anti-RNP+ was associated with worse progression-free survival on multivariable analysis (HR 1.44, 95% CI 1.02, 2.03), but not univariate. Although anti-MDA5+ was associated with early mortality, there was a non-significant trend for improved progression-free survival (adjusted HR 0.24, 95% CI 0.05, 1.10). Of note, only 1/9 MDA-5 patients with <3 months survival mortality had ever had lung function tests.

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Table 1. Comparison of baseline characteristics between broader or key antibody groups. The tests used were χ^2d for categorical or Kruskal–Wallace for continuous variables. Statistically significant results are highlighted in bold typeface. The final column indicates the overall distribution of the baseline characteristics for the whole cohort. Data for smaller antibody groups are not presented here. Data are presented as median (interquartile range) for CK, CRP, and follow-up duration; all others are presented as % (number of patients) or mean (S.D.).

Baseline characteristic	Jo-1 ($n = 121$)	Other ARS ($n = 90$)	MDA-5 ($n = 31$)	Isolated Ro52 ($n = 51$)	Sero-negative ($n = 32$)	*P*-value	Overall ($n = 430$)
Age at presentation	52.1 (12.5)	51.4 (14.9)	47.6 (9.3)	58.4 (13.8)	51.8 (14.3)	**0.017**	52.6 (14.1)
Males	31% (38)	24% (22)	32% (10)	31% (16)	41% (13)	0.38	32% (139)
Ethnicity:						0.73	
Caucasian	50% (60)	46% (41)	48% (15)	53% (27)	38% (12)		46% (196)
Other	33% (40)	42% (38)	42% (13)	35% (18)	47% (15)		39% (168)
Unknown	17% (21)	12% (11)	10% (3)	12% (6)	16% (5)		15% (66)
Smoking status:						0.73	
Never	70% (70)	64% (50)	74% (14)	74% (35)	71% (17)		68% (239)
Smoker (ex or current)	30% (30)	36% (28)	26% (5)	26% (12)	29% (7)		32% (112)
BMI (kg/m^2)	29.0 (6.3)	29.0 (6.4)	24.9 (5.3)	30.0 (7.5)	28.3 (6.5)	**0.033**	28.4 (6.4)
IPAF-MSA	0.8% (1)	28.1% (27)	3.2% (3)	45.1 (23)	0% (0)	**<0.001**	56 (13%)
CK (U/l)	190.0 (87.0-723.0)	141.0 (68.0-408.0)	94.0 (38.0-161.0)	112.5 (57.0-197.0)	564.0 (50.0-1324.0)	**<0.001**	160.0 (69.0-562.0)
CRP (U/l)	7.9 (3.0–22.0)	8.5 (2.0–24.0)	6.3 (2.0–32.0)	5.5 (2.0–11.0)	9.0 (3.0–16.0)	0.26	6.5 (2.0–17.0)
Baseline %Pred FVC	72.5 (21.3)	70.8 (22.7)	76.1 (19.2)	77.3 (24.9)	71.7 (18.8)	0.66	73.3 (21.7)
Baseline %Pred FEV1	71.3 (19.4)	69.3 (21.3)	74.1 (18.8)	75.6 (22.7)	71.8 (17.3)	0.58	72.1 (20.6)
Baseline %Pred TLCO	47.1 (17.4)	41.9 (15.2)	48.7 (15.3)	45.9 (20.2)	41.1 (17.8)	0.23	45.0 (17.7)
Baseline %Pred KCO	79.8 (16.6)	74.0 (17.5)	78.5 (16.9)	70.4 (18.6)	72.9 (17.5)	**0.031**	76.3 (17.6)
Treated with rituximab or CYC in first 6 months	36.4% (44)	32.2% (29)	64.5% (20)	25.5% (13)	28.1% (9)	**0.002**	32.8 (141)
Prednisolone dose at 2 years (mg)	8.5 (8.4)	7.9 (6.2)	6.8 (5.5)	6.5 (4.7)	6.5 (5.4)	0.42	7.6 (6.6)
Charlson Comorbidity Index	1.1 (0.7)	1.1 (0.9)	0.9 (0.5)	0.8 (0.7)	1.1 (0.4)	0.30	1.1 (0.8)
Malignancy	2.5% (3)	5.6% (5)	3.2% (1)	0.0% (0)	3.1% (1)	0.42	3.7% (16)
PASP > 30 mmHg	7.4% (9)	12.2% (11)	0.0% (0)	23.5% (12)	12.5% (4)	**0.005**	9.8% (42)
Clinical CTD overlap	4.1% (5)	11.1% (10)	3.2% (1)	13.7% (7)	12.5% (4)	**<0.001**	11.4% (49)
Hospitalized in 1st month	17.8% (18)	13.9% (11)	50.0% (13)	10.9% (5)	21.7% (5)	**<0.001**	18.0% (66)
Follow-up duration (years)	5.4 (3.1–8.4)	4.4 (2.9–6.9)	3.4 (0.1–5.7)	3.2 (1.8–5.8)	4.4 (1.9–8.6)	**0.002**	4.3 (2.4–7.3)
Died	14.0% (17)	21.1% (19)	32.3% (10)	21.6% (11)	21.9% (7)	0.20	22.1% (95)
Meets secondary end point	19.0% (23)	23.3% (21)	22.6% (7)	17.6% (9)	15.6% (5)	0.91	20.2% (87)

[a] Charlson score amended to exclude age criteria, as this was adjusted for separately. PASP: pulmonary arterial systolic pressure; IPAF: interstitial pneumonia with autoimmune features; CK: creatine kinase; FVC: forced vital capacity; %pred: percentage of predicted value; TLCO: carbon monoxide transfer test; FEV1: forced expiratory volume in 1 second; KCO: carbon monoxide transfer coefficient.

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Table 2. Univariate and multivariate Cox modelling for all-cause mortality hazard ratio according to baseline characteristics. Multivariate model is adjusted for age, gender, ethnicity, malignancy, smoking status, CTD overlap, and hospital site. Statistically significant results are highlighted in bold type

Baseline variable	Univariate model		Multivariate model	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age	1.04 (1.02, 1.06)	**<0.001**	1.04 (1.02, 1.05)	**<0.001**
Male	1.50 (1.00, 2.26)	0.520	1.41 (0.85, 2.36)	0.186
Caucasian	1.44 (0.92, 2.25)	0.111	0.87 (0.62, 1.22)	0.433
Malignancy	1.80 (0.78, 4.12)	0.166	1.33 (1.01, 1.75)	**0.041**
PASP > 30 FEV1	2.58 (1.55, 4.28)	**<0.001**	2.23 (1.27, 3.93)	**0.005**
Charlson Comorbidity Index[a]	1.33 (1.07, 1.63)	**0.007**	1.26 (1.20, 1.32)	**<0.001**
Current or ex smoker	2.83 (1.71, 4.71)	**<0.001**	2.42 (1.67, 3.50)	**<0.001**
Clinical CTD overlap	1.40 (0.82, 2.36)	0.214	1.56 (1.07. 2.29)	**0.022**
BMI	0.94 (0.90, 0.98)	**0.005**	0.93 (0.84, 1.04)	0.193
IPAF	1.18 (0.64, 2.17)	0.591	0.84 (0.42, 1.70)	0.634
CK	1.00 (1.00, 1.00)	0.187	1.00 (1.00, 1.00)	0.540
CRP	1.01 (1.00, 1.01)	**0.001**	1.01 (1.00, 1.01)	**<0.001**
ESR	1.01 (1.00, 1.01)	0.117	1.01 (1.00, 1.02)	**0.010**
Baseline FVC (%pred)	0.99 (0.98, 1.00)	0.083	0.98 (0.97, 099)	**<0.001**
Baseline TLCO (%pred)	0.97 (0.96, 0.99)	**0.001**	0.97 (0.96, 0.99)	**<0.001**
Baseline FEV1 (%pred)	0.99 (0.97, 1.00)	**<0.001**	0.98 (0.96, 0.99)	**<0.001**
Baseline KCO (%pred)	0.98 (0.97, 1.00)	0.053	0.98 (0.98, 1.00)	**0.004**
Rituximab or CYC in first 6 months	0.89 (0.57, 1.39)	0.607	1.06 (0.83, 1.35)	0.635
Prednisolone dose at 2 years	1.02 (0.99, 1.06)	0.244	1.04 (1.01, 1.07)	**0.005**
Hospitalized in first month	1.71 (1.06, 2.78)	**0.028**	2.09 (0.98, 4.48)	0.057

[a] The Charlson score was amended to not include age, as this was adjusted for separately. PASP: pulmonary arterial systolic pressure; IPAF: interstitial pneumonia with autoimmune features; CK: creatine kinase; FVC: forced vital capacity; %pred: percentage of predicted value; TLCO: gas transfer test; FEV1: forced expiratory volume in 1 second; KCO: carbon monoxide transfer coefficient; HR: hazard ratio.

Lung-function trends over time

Multilevel mixed-effects regression (shown in Fig. 3) indicated that, after the first 6 months, there was a longitudinal trend towards worsening %FVC in anti-PL7+ IIM-ILD, whereas a continuous gradual %FVC improvement was seen with anti-MDA5+ over the first 3 years. Longitudinal %FVC trends were no different in anti-Jo1+ *vs* negative patients. Although %FVC appeared lower over 3 years in anti-Ku–, PL12- and Ro52-positive patients compared with their respective antibody-negative counterparts, the CIs of modelled lines overlapped, indicating they were not significantly different (Supplementary Fig. S3, available at *Rheumatology* online). Changes in %TLCO over time by antibody showed similar trends but were not statistically significantly different from each other (Supplementary Fig. S4, available at *Rheumatology* online). Due to missing lung function data, fewer subjects contributed to these analyses than contributed to the survival analyses (Supplementary Table S1, available at *Rheumatology* online).

Post-hoc analyses were performed to explore the impact of survivor bias on %FVC trend. Supplementary Fig. S5 (available at *Rheumatology* online) shows all individual subject's FVC trends over time. There appeared to be a slight improvement in lung function in survivors in the 10 years preceding censoring that was not apparent in patients experiencing death or transplant, supporting the hypothesis that trends in lung function may differ between survivors and non-survivors.

Joint modelling of longitudinal trends in %FVC and survival, looking specifically at anti-MDA5 (Supplementary Fig. S6, available at *Rheumatology* online), demonstrated that, while %FVC in anti-MDA5–negative patients increased minimally (0.27 per year, $P = 0.117$) in anti-MDA5+ patients, the rate of increase was significantly higher (4.21 per year, $P < 0.001$; test for interaction $P < 0.001$). This corroborated the significance of the trends seen on multi-level mixed-effect modelling, suggesting that early mortality in anti-MDA5+ is not largely contributing to the improvement in anti-MDA5+ %FVC with time.

Discussion

To our knowledge, this is the largest study to analyse the prognostic relevance of autoantibodies in a European cohort of IIM-ILD patients. The imbalance of baseline characteristics between antibody groups and exploration of these variables by univariate Cox regression suggested that several of these characteristics may be important mortality risk factors. Previous meta-analysis had also demonstrated age, acute presentation, lower FVC and TLCO and higher CRP to be associated with increased mortality [5]. We additionally demonstrated increased mortality risk in current/ex-smokers and in patients with a PASP of >30 mmHg. In keeping with our findings, smoking has well established links with mortality in other lung diseases [18], and PAH is more common and convincingly associated with mortality in other CTDs such as SSc [19].

Anti-synthetases

Mortality was increased in patients with anti-PL7. In contrast to the early (<3 months) mortality demonstrated in anti-MDA5+ IIM-ILD, the Kaplan–Meier curve for PL-7 appeared to deviate more clearly from that of the other antibodies after 3 years. However, the number of patients included in the anti-PL7+ analysis had reduced to only 16 at 3 years, and therefore further statistical analysis on this was not pursued and this should be interpreted with caution. Although progression-free survival also appeared reduced in

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Table 3. Results of univariate and multivariate Cox survival models for primary (all-cause mortality) and secondary (progression-free survival) end points. Note that the number of patients included in the secondary end point analysis was lower, because this was designed to primarily look at lung function deterioration, so patients without repeated measures of lung function could not be included. Statistically significant results are highlighted in bold type

Antibody	Number of patients	Number reaching end point	Univariate model		Multivariate model	
			HR (95% CI)	*P* value	HR (95% CI)	*P* value
Primary end point—all-cause mortality						
Jo1	126	21	0.56 (0.35, 0.91)	**0.020**	0.61 (0.42, 0.87)	**0.006**
PL12	44	10	0.90 (0.47, 1.73)	0.748	1.06 (0.90, 1.26)	0.482
PL7	26	11	2.29 (1.22, 4.31)	**0.010**	2.06 (1.42, 2.99)	**<0.001**
EJ	16	2	0.63 (0.15, 2.56)	0.517	0.65 (0.30, 1.38)	0.262
OJ	9	1	0.51 (0.07, 3.68)	0.505	0.42 (0.22, 8.01)	0.562
Mi2	19	4	1.31 (0.48, 3.58)	0.603	0.89 (0.27, 2.90)	0.846
SRP	16	3	1.00 (0.32, 3.17)	1.000	0.81 (0.17, 3.76)	0.783
MDA5 (first 3 months)	32	9	65.2 (14.1, 302.0)	**<0.001**	482.4 (1.4, 22386.1)	**0.002**
MDA5 (after 3 months)	23	2	0.55 (0.14, 2.28)	0.419	0.85 (0.27, 2.70)	0.781
PMScl	40	8	0.89 (0.43, 1.85)	0.764	0.65 (0.40, 1.06)	0.086
RNP	30	12	1.48 (0.80, 2.72)	0.208	1.90 (1.24, 2.93)	**0.003**
Ku	13	3	1.16 (0.37, 3.66)	0.804	1.81 (0.37, 8.85)	0.463
Negative	32	7	0.96 (0.45, 2.08)	0.924	0.90 (0.49, 1.65)	0.733
Ro52	195	40	1.13 (0.75, 1.70)	0.568	1.15 (0.74, 1.79)	0.523
All ARS	215	39	0.58 (0.38, 0.87)	**0.009**	0.64 (0.52, 0.77)	**<0.001**
Secondary end point—deterioration in lung function, transplant, or death						
Jo1	114	25	0.79 (0.49, 1.28)	0.347	0.80 (0.44, 1.43)	0.447
PL12	39	11	1.31 (0.69, 2.48)	0.405	1.38 (0.94, 2.02)	0.103
PL7	25	8	2.07 (1.00, 4.31)	0.051	1.89 (0.87, 4.11)	0.109
EJ	15	1	0.47 (0.07, 3.41)	0.459	0.51 (0.03, 8.71)	0.642
OJ	9	2	0.58 (0.08, 4.19)	0.591	0.54 (0.06, 5.00)	0.590
Mi2	15	1	0.53 (0.07, 3.79)	0.524	0.50 (0.02, 13.01)	0.675
SRP	15	3	1.05 (0.33, 3.33)	0.933	0.82 (0.56, 1.20)	0.300
MDA5	31	8	0.23 (0.03, 1.62)	0.139	0.24 (0.05, 1.10)	0.066
PMScl	35	8	0.87 (0.38, 2.00)	0.734	0.93 (0.34, 2.59)	0.895
RNP	26	10	1.36 (0.68, 2.73)	0.385	1.44 (1.02, 2.03)	**0.036**
Ku	12	6	2.98 (1.29, 6.87)	**0.010**	3.99 (0.87, 18.36)	0.076
Negative	30	5	0.85 (0.34, 2.10)	0.730	0.89 (0.44, 1.84)	0.773
Ro52	82	41	1.29 (0.83, 2.01)	0.262	1.31 (0.71, 2.44)	0.378
All ARS	197	44	1.00 (0.64, 1.54)	0.966	0.99 (0.74, 1.32)	0.943

HR: hazard ratio; ARS: anti-tRNA-synthetases.

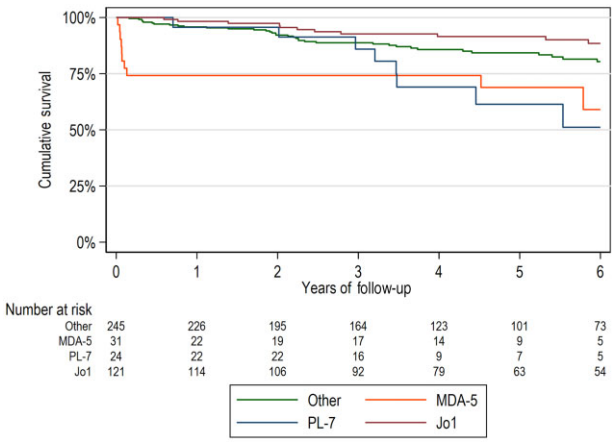

Figure 1. Kaplan–Meier curve showing mortality by key antibodies to: MDA-5, PL-7 and Jo-1. This chart demonstrates the number at risk contributing to the analysis for each group in the table below. Early mortality is clearly demonstrated in the anti-MDA5 group

patients with anti-PL7+, this did not reach statistical significance, but graphical modelling of %FVC over time did demonstrate a later more evident deterioration in FVC in this group compared with that for other antibodies from 6 months onwards. In contrast, anti-Jo1, another ARS, was associated with a consistently reduced risk of mortality across univariate and multivariate models. Given that anti-Jo1 was the most frequent ARS, the combined ARS+ group was characterized by better survival compared with ARS-negative patients, despite the increased mortality seen in anti-PL7+.

Given the rarity of individual ARS antibodies, most observational studies reporting outcomes by antibody have grouped anti-synthetases together. However, the findings are not necessarily generalizable across the anti-synthetase antibodies. In a previous study by Shi *et al.*, a non-significant trend towards higher early mortality in anti-PL7 was observed [20], and an increased risk of pulmonary function deterioration was observed by Fujisawa *et al.* [21]. By contrast, Marie *et al.* grouped anti-PL7/PL12 together and found no difference in mortality compared with anti-Jo1. However, they did find ILD was more prevalent in anti-PL7/PL12- than in anti-Jo1–positive patients, was more likely to be symptomatic at diagnosis, had higher median HRCT (High-resolution computed tomography) fibrosis scores at diagnosis, and was less likely to undergo radiological resolution [22]. Hervier *et al.*'s cluster analysis of clinical features of a group of 233 ASS patients in France, identified three phenotypic patterns: one highly specific to anti-Jo1 with diffuse anti-synthetase manifestations, a second cluster containing 96% of their anti-

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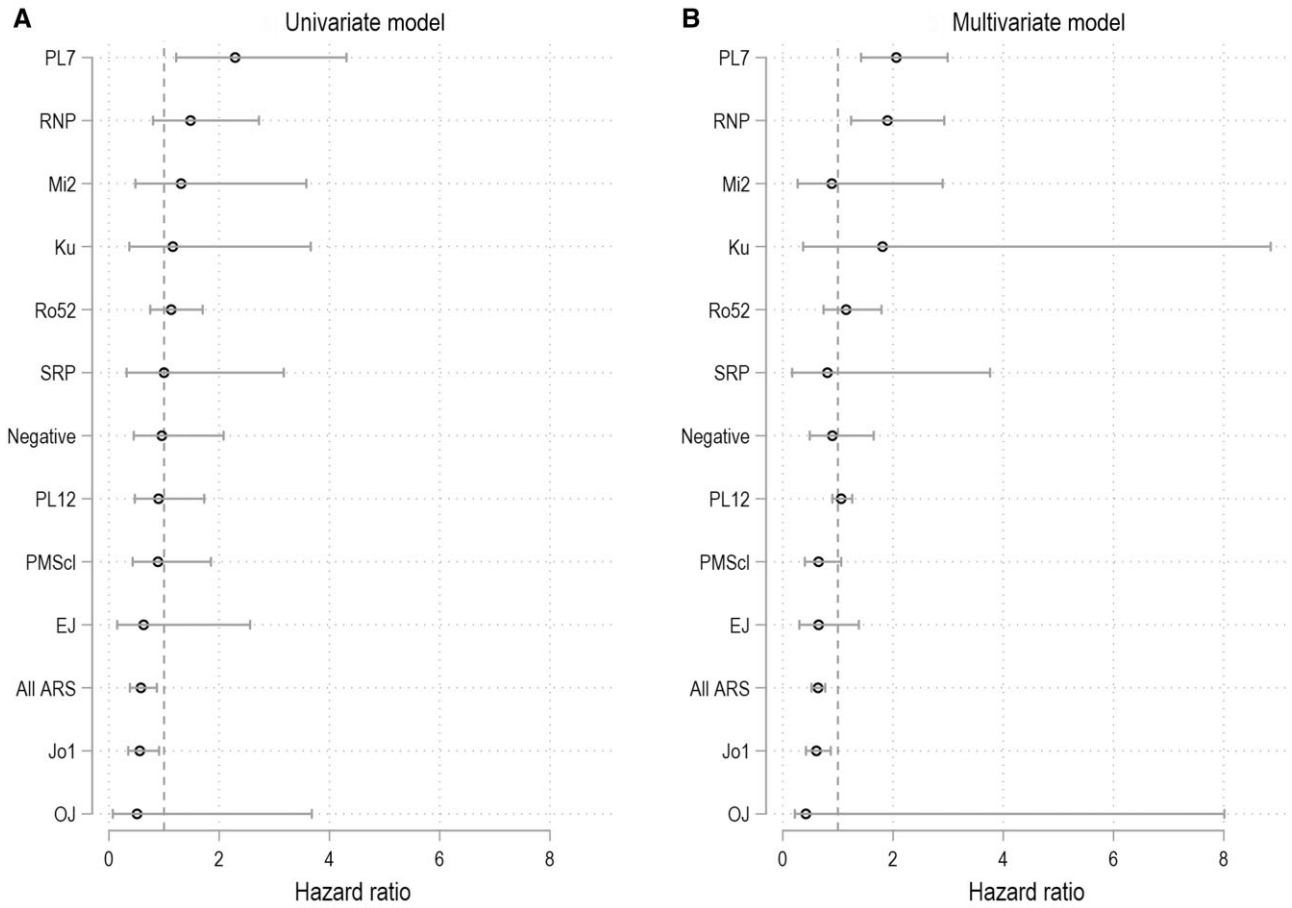

Figure 2. Hazard ratios for all-cause mortality. Univariate and multivariate models demonstrating hazard ratios and 95% CIs for the primary end point of all-cause mortality according to antibody, *vs* all other antibodies. The dashed line represents hazard ratio = 1. (A) Unadjusted model (B) Adjusted multivariate model for age, sex, ethnicity, malignancy, clinical CTD overlap status, and hospital site. Anti-MDA5 has been excluded from this figure due to non-proportionality of the hazards

PL7/PL12 patients, with largely isolated ILD, and a third cluster comprising patients with anti-RNP or SLE overlap antibodies, with high frequencies of RP and cutaneous manifestations. This suggests anti-PL7+ and anti-PL12+ patients are similar to each other, yet distinct from anti-Jo1 patients. Overall, they found survival to be significantly lower in patients with anti-PL7/PL12 than with anti-Jo1 antibodies, on bivariate analysis, although statistical significance was lost on multivariate modelling [23]. Our study did not detect any differences in primary or secondary outcomes or lung function trends over time in patients with anti-PL12+. Although we cannot exclude the possibility that this could be related to insufficient sample size, anti-PL12 was our third-most-frequent antibody, and significant differences were detected in antibodies occurring at lower frequencies (i.e. antibodies to RNP, PL7 and Ku). Our results suggest that PL-7 and PL-12 may not be as similar as previously thought. There may be a phenotypic difference between them, with PL-7 potentially having a greater propensity towards fibrotic progression. However, our results are based on moderate numbers, and the findings would need to be confirmed in a separate set, ideally with larger numbers.

Anti-MDA5

The existing literature provides a strong narrative of acute presentations with high mortality in anti-MDA5+ disease [24–27]. Our data supported this, but also demonstrated that most MDA5-related deaths occurred within 3 months, highlighting the extremely high early mortality of the disease. By contrast, analysis of lung function trends showed that %FVC improved with anti-MDA5 over time significantly more than in MDA5-negative disease, suggesting that survivors of early mortality may be more likely to subsequently follow a stable or improving clinical path. However, the interpretation of our findings is limited by the fact that those presenting acutely (i.e. those dying early in the disease course) may have been too unwell to ever record lung function or to have repeated measures over time. Indeed, 8 of our 9 MDA5+ patients who died within the first 3 months never had any lung function measurements. Additionally, although the last recorded lung function was taken as a surrogate marker for lung function at time of death, this may not have been accurate, as the available data do not allow model trends occurring shortly before death to be seen.

Although our data can only suggest a pattern of disease behaviour, rather than lead to conclusive findings, this study suggests that anti-MDA5+ patients surviving the first 3 months, (either because they get through the fulminant stage or because they present with a more chronic, indolent presentation), may progressively experience improvement in lung function and have a good prognosis. By contrast, anti-PL7+ patients appear more likely to progressively lose lung function

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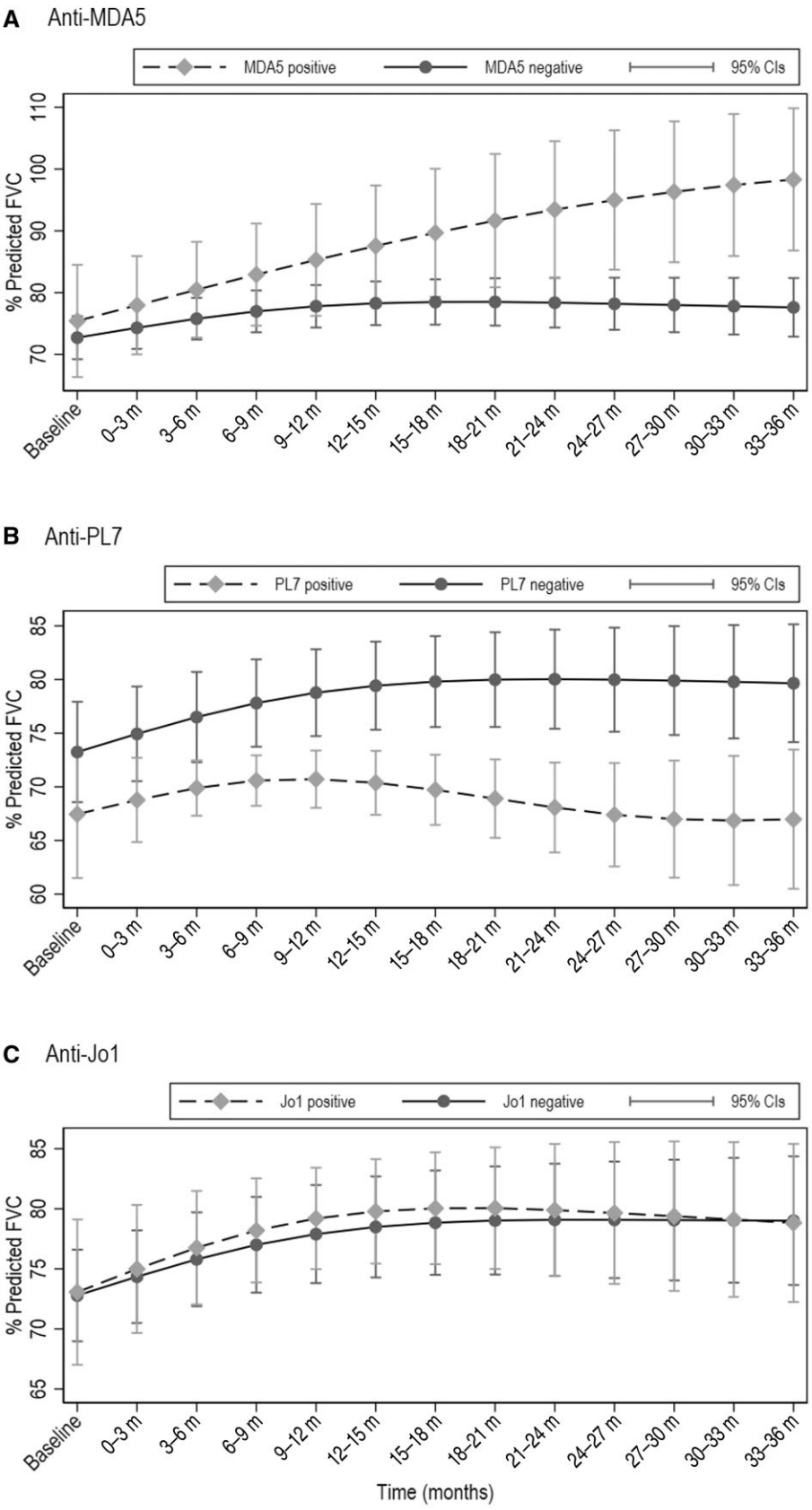

Figure 3. Trend in FVC over time in (A) MDA-5, (B) PL-7, and (C) Jo1. The data model shows improvement of %pred FVC in anti-MDA5+ compared with anti-MD5–negative patients, which becomes more evident from 2 years onwards, whereas %pred FVC in anti-PL7+ patients appears lower than in anti-PL7–negative patients. The anti-Jo1+ pattern of %pred FVC over time does not appear to differ from that of anti-Jo1–negative patients. FVC: FVC: forced vital capacity; %pred: percentage of predicted value

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and may have higher later mortality than other patient groups.

Despite previously demonstrated poor prognosis, our findings point to the existence of a group of anti-MDA5+ patients with ILD who do well. The existence of different prognostic groups has also been observed by Allenbach *et al.*, who identified a cluster of anti-MDA5+ patients with rapidly progressive ILD, a second cluster (with predominant dermatorheumatological symptoms) with good prognosis, and a third cluster (with severe skin vasculopathy) with intermediate prognosis [28].

Overlap CTD

Anti-RNP, commonly associated with a mixed CTD phenotype, was significantly associated with mortality in the multivariate model. Anti-Ku, also associated with overlap CTD, was associated with reduced progression-free survival on univariable analysis only, suggesting either lack of true association or that the statistical power was too low to detect a difference on multivariate analysis. Although multivariate modelling accounted for clinical overlap status, the retrospective study design meant the presence of overlap conditions was potentially underrecognized in our cohort, either remaining undiagnosed by the physician or through inadequate contemporaneous record taking. Additionally, even in the absence of other clinical overlap features, clinicopathological features of anti-RNP+ or anti-Ku+ ILD may align more closely with an SSc or RA-ILD phenotype, either of which are thought to have a worse prognosis than IIM-ILD [29]. While maximally adjusted models did not support suspected PAH to be the cause of the increased mortality in the anti-RNP+ group, our use of a pragmatic surrogate marker for PAH, rather than right-heart catheterization results, means true cases of PAH may not have been accurately identified, and therefore PAH may still underlie the increased mortality in the anti-RNP+ group.

Overlap CTD groups remain relatively understudied. The largest study on anti-Ku+ IIM-ILD showed that 6 out of 8 anti-Ku+ patients with IIM and ILD were deemed to have CS-resistant disease [30]. Our findings of a possible, though inconsistent, association with mortality or progression with anti-RNP and anti-Ku, respectively, highlighted the fact that further research in this area is needed.

Ro52

Anti-Ro52 has previously been linked with poor prognosis [31]. We did not identify any association with either mortality, progression-free survival, or differential lung function patterns over time, compared with anti-Ro52–negative IIM-ILD.

Limitations

Despite being one of the largest described cohorts of IIM-ILD, the numbers of patients within certain antibody groups remained low, such that we cannot exclude a lack of statistical power for detecting small differences between groups. There is a limitation due to the retrospective design of the study, and associated potential recall bias and missing data. However, variables with lower susceptibility to bias were focused upon. Many metrics were extracted directly from the electronic health records, e.g. lung function, demographics, biomarkers and mortality, thereby strengthening confidence in the retrospective analysis. However, collection of data on other organ involvement was not possible due to lack of detail in the historical clinical notes. For example, our surrogate definition of possible co-existent pulmonary hypertension of PASP $>$ 30 mmHg was a pragmatic (but imperfect) solution based on the available data. Right heart catheterization for the diagnosis of PAH is an underutilized investigation, with too few patients referred for this test, and long delays in awaiting the procedure. In contrast, almost all patients undergo an echocardiogram within the first year of diagnosis.

Cardiac manifestations, dysphagia, and muscle strength are potential confounders that were not captured. Adjustment was not made for treatment differences, or for considering that the main drivers of treatment would have been severity and rate of progression rather than antibody profile. Reassuringly, sensitivity analysis adding baseline disease severity markers to the adjusted models did not change the significance of the results, suggesting that the link between antibody and outcome was independent of disease severity markers such as lung function, inflammation burden, and pulmonary hypertension.

The impact of missing data in multivariate models was minimized using multiple imputation. Using mixed-effect models for repeated measures over time for lung function trend analysis allowed inclusion of more data than if fixed intervals had been used.

As with all retrospective studies, differential loss to follow-up could have introduced bias. Using a multicentre design reduced the impact of the variation in local care practices on results, or loss to follow-up to other regional centres. All three included sites were city-centre, tertiary specialist centres, and therefore the case mix referred to these centres may not necessarily reflect those encountered in other geographical areas, with a potential bias towards more severe disease.

No correction for multiple comparisons was made in the analyses. It is therefore possible that some statistically significant findings could be due to chance. However, this study guides further research by highlighting relevant areas to consider in future prospective research.

Conclusion

This study suggests several important prognostic factors in a large, real-world group of patients. IIM-ILD patients with anti-MDA5 and anti-PL7 are at highest risk of mortality, although survivors of the early peak in mortality of anti-MDA5+ disease appear to have a good prognosis. Patients with anti-RNP may also be at higher risk. By contrast, anti-Jo1 is comparatively protective. The difference between prognosis with anti-Jo1 and anti-PL7 positivity highlights the need to consider subgrouping anti-synthetase syndrome in both clinical research and clinical practice.

Except for early mortality in anti-MDA5, it is important to acknowledge that the magnitude of difference in outcomes between the antibody subtypes is small in absolute terms. The differences attributable to antibodies alone should not be the sole determinant of treatment intensity but need to be interpreted in the context of the entire patient phenotype. However, vigilance must remain high for the acute presentation of anti-MDA5+ IIM-ILD, which has consistently been shown to have high associated mortality.

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Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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