RHEUMATOLOGY

Rheumatology 2018;57:1212–1221
doi:10.1093/rheumatology/key060
Advance Access publication 27 March 2018

Original article

Initial predictors of poor survival in myositis-associated interstitial lung disease: a multicentre cohort of 497 patients

Shinji Sato[1,*], Kenichi Masui[2,3,*], Naoshi Nishina[4], Yasushi Kawaguchi[5], Atsushi Kawakami[6], Maasa Tamura[7], Kei Ikeda[8], Takahiro Nunokawa[9], Yoshinori Tanino[10], Katsuaki Asakawa[11], Yuko Kaneko[12], Takahisa Gono[4,13], Taro Ukichi[14], Shinjiro Kaieda[15], Taio Naniwa[16] and Masataka Kuwana[4]; A Multicentre Retrospective Cohort of Japanese Patients with Myositis-associated ILD Investigators[a]

Abstract

Objective. To identify initial predictors of poor survival in patients with PM/DM-associated interstitial lung disease (ILD).

Methods. We established a multicentre retrospective cohort of incident cases of PM/DM-associated ILD from 44 institutions across Japan (Multicentre Retrospective Cohort of Japanese Patients with Myositis-associated ILD, JAMI). Inclusion criteria were an onset age $\geqslant$16 years; PM/DM or clinically amyopathic DM according to the published criteria; imaging evidence of ILD; and availability of serum samples for assays of autoantibodies such as anti-melanoma differentiation-associated gene 5 and anti-aminoacyl tRNA synthetase. We collected demographic data and clinical characteristics recorded at the time of diagnosis, as well as follow-up survival data. Predictors of ILD-related mortality were identified by univariate and multivariate analyses.

Results. JAMI enrolled a cohort of 497 patients with PM (15%), classic DM (32%) and clinically amyopathic DM (53%). During the observation period (median 20 months), 76 died of respiratory insufficiency directly related to ILD. Univariate analysis revealed several initial parameters associated with ILD mortality, including demographic, clinical, laboratory, imaging and autoantibody variables. We used multivariate analysis with a stepwise selection of parameters to generate an appropriate predictive model, and identified the following independent risk factors for ILD mortality: age at onset $\geqslant$60 years [hazard ratio (HR) = 4.3, 95% CI: 2.4, 7.5], CRP $\geqslant$1 mg/dl (HR = 2.6, 95% CI: 1.5, 4.8), peripheral capillary oxygen saturation $<$95% (HR = 2.0, 95% CI: 1.2, 3.4) and anti-melanoma differentiation-associated gene 5 antibody (HR = 7.5, 95% CI: 2.8, 20.2).

CLINICAL SCIENCE

[1]Division of Rheumatology, Department of Internal Medicine, Tokai University School of Medicine, Kanagawa, [2]Department of Anaesthesiology, National Defence Medical College School of Medicine, Saitama, [3]Department of Anesthesiology, Showa University School of Medicine, [4]Department of Allergy and Rheumatology, Nippon Medical School Graduate School of Medicine, [5]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, [6]Unit of Translational Medicine, Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, [7]Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, Yokohama, [8]Department of Allergy and Clinical Immunology, Chiba University Hospital, Chiba, [9]Department of Rheumatic Diseases, Tokyo Metropolitan Tama Medical Centre, Tokyo, [10]Department of Pulmonary Medicine, Fukushima Medical University School of Medicine, Fukushima, [11]Division of Respiratory Medicine, Niigata University Medical and Dental Hospital, Niigata, [12]Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, [13]Department of Rheumatology, Saitama Medical Centre, Jichi Medical University, Saitama, [14]Division of Rheumatology, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, [15]Department of Medicine, Division of Respirology, Neurology, and Rheumatology, Kurume University School of Medicine, Fukuoka and [16]Division of Respiratory Medicine, Allergy and Rheumatology, Nagoya City University School of Medicine, Aichi, Japan

Submitted 22 October 2017; revised version accepted 8 February 2018

*Shinji Sato and Kenichi Masui contributed equally to this study.

[a]See Acknowledgements section for a list of other JAMI investigators.

Correspondence to: Masataka Kuwana, Department of Allergy and Rheumatology, Nippon Medical School Graduate School of Medicine, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan.
E-mail: kuwanam@nms.ac.jp

Conclusion. We established a large cohort of incident cases of PM/DM-associated ILD, and successfully identified independent predictors of short-term ILD mortality.

Key words: myositis and muscle disease, respiratory, autoantigens and autoantibodies, outcome measures, biomarkers

Rheumatology key messages

- Early death due to respiratory insufficiency is common in myositis-associated interstitial lung disease.
- Anti-melanoma differentiation-associated gene 5 antibody is the most powerful initial predictor of myositis-associated interstitial lung disease mortality.
- Independent predictors of myositis-associated interstitial lung disease mortality include older age and high CRP.

Introduction

PM and DM are autoimmune conditions classified into a group of idiopathic inflammatory myopathies that target muscle, skin, joints and lungs to various degrees [1]. Interstitial lung disease (ILD) is a life-threatening complication in PM/DM [2]. The clinical course and treatment response of PM/DM-associated ILD are quite heterogeneous, with the most devastating form being rapidly progressive ILD (RP-ILD), which is often resistant to immunosuppressive treatment [3, 4]. Approximately half of the patients who develop RP-ILD die despite intensive immunosuppressive treatment [5, 6]. Although an evidence-based treatment strategy has not been established for RP-ILD, studies suggest that it may be beneficial to introduce intensive immunosuppressive therapy, such as high-dose CS in combination with immunosuppressive agents, at an early stage of the disease, before the lungs are irreversibly damaged [7, 8]. Thus, it is critical to identify predictive factors of poor survival in patients with PM/DM-associated ILD.

A number of studies have examined potential risk factors associated with poor survival in patients with PM/DM-associated ILD, and have reported associations between poor outcomes and older age, DM classification, skin ulceration, pneumomediastinum and a lack of myositis [9–11]. Among the myositis-specific autoantibodies (MSAs), anti-melanoma differentiation-associated gene 5 (MDA5) and anti-aminoacyl tRNA synthetase (ARS) antibodies are associated with ILD, but RP-ILD is more likely to be associated with anti-MDA5 antibody [5, 6, 12, 13]. A series of studies have reported that anti-MDA5 antibody, acute or subacute ILD onset, fever, higher serum ferritin levels, decreased circulating lymphocyte counts, elevated serum CRP and a lower consolidation/ground-glass attenuation (GGA) pattern on chest high-resolution CT (HRCT) are independent risk factors for predicting the course of RP-ILD or mortality [14–19]. While anti-MDA5 antibody is consistently reported as a poor survival factor in most studies [13], other reported prognostic factors are less consistent, probably due to the small sample sizes of these single-centre studies and to differences in patient populations between studies. To overcome these limitations, it was necessary to design a large-scale, well-defined, multicentre cohort.

To that end, we established the Multicentre Retrospective Cohort of Japanese Patients with Myositis-associated ILD (JAMI), which involved 44 institutions across Japan with a wide range of specialties, including rheumatology, respirology and dermatology. Information for the cohort was collected from demographic, clinical, imaging and laboratory data at the time of diagnosis, as well as autoantibody profiles, and the clinical course was retrospectively and/or prospectively recorded. Using the data from 497 incident cases of adult PM/DM-associated ILD registered in the JAMI database, we identified initial factors that predict mortality from respiratory insufficiency due directly to ILD.

Methods

Patients

JAMI is a multicentre retrospective cohort that allowed collaborative research on PM/DM-associated ILD. Investigators in individual participating centres were asked to enrol incident PM/DM-associated ILD cases who visited their centres between October 2011 and 2015. The inclusion criteria were as follows: an age at disease onset $\geqslant$16 years; definite or probable PM/DM according to the criteria proposed by Bohan and Peter [20] or clinically amyopathic DM (CADM) according to the criteria proposed by Sontheimer [21]; the presence of ILD, based on the American Thoracic Society criteria and a multidisciplinary assessment of clinical, radiologic and pathologic findings [22]; and availability of serum samples at diagnosis for comprehensive MSA analysis. At enrolment, data were collected retrospectively in a dedicated electronic database by a reference clinician in each centre. To evaluate outcomes, follow-up survival data, any diagnosis of malignancy and the cause of death if deceased were collected prospectively. This study was approved by the Ethics Committee of the coordinating centre (Nippon Medical School, Tokyo, Japan; 26-03-434) and by individual participating centres. All clinical information was obtained after the patients had given their informed consent. The JAMI cohort is registered in the University Hospital's Medical Information Network Clinical Trial Registry (UMIN000018663).

JAMI database

At enrolment, demographic, clinical, laboratory and imaging information at the time of diagnosis, before beginning immunosuppressive treatment, was inputted. The following demographic and clinical data were collected: gender, age at disease onset, body weight, height, postal code of residence at disease onset, disease duration at diagnosis, initial symptoms related to the disease, disease classification (PM, classic DM or CADM), fever, arthritis/arthralgia, Raynaud's phenomenon, sclerodactyly, sicca, muscle weakness, myalgia, Gottron's papules, Gottron's sign, palmar papules, heliotrope rash, shawl sign, neck V-sign, flagellate erythema, skin ulceration, periungual erythema, mechanic's hands and subcutaneous calcinosis. Peripheral blood laboratory results were recorded, including creatine kinase, aldolase, CRP, ESR, Krebs von den Lungen-6 (KL-6), surfactant protein D (SP-D), ferritin, Raynaud's phenomenon and ANAs on IIF. Findings on electromyography, MRI of extremities, chest radiograph, chest HRCT, peripheral capillary oxygen saturation (SpO_2), arterial blood gas analysis, forced vital capacity, forced expiratory volume in 1 s, diffusing capacity for carbon monoxide, 6-min walking distance, and pathologic findings of skeletal muscle, skin and lung were also collected when available. Chest HRCT findings were classified into four patterns according to Tanizawa *et al.* [23]: lower lobe consolidation/GGA, lower lobe reticulation, random GGA and others. The induction treatment regimen was also recorded, including CS (with starting dosage), CS pulse therapy, CYC, CSA, tacrolimus, MTX, AZA, MMF, IVIG and other treatments. A prednisolone equivalent of $\geqslant$50 mg daily was regarded as high-dose CS. We examined the patient's records from diagnosis until the last visit, and recorded the cause of death if the patient was deceased.

MSA detection

Serum samples were stored at -20°C until use. MSAs were identified centrally at laboratories with the proper expertise at Tokai University, Keio University or Nippon Medical School. Anti-ARS antibodies were detected by RNA immunoprecipitation assay using K562-cell extracts as described previously [24]. Anti-ARS antibody results were judged positive when the given serum samples precipitated RNA components identical to those precipitated by the prototype sera positive for anti-Jo-1, anti-EJ, anti-OJ, anti-PL-7, anti-PL-12 or anti-KS. The anti-MDA5 antibody was measured by an in-house ELISA using recombinant MDA5 as an antigen source [25].

Statistical analysis

We conducted univariate and multivariate analyses to identify predictive factors of mortality due to respiratory insufficiency directly related to PM/DM-associated ILD. Continuous values were shown as the median and 2.5–97.5 percentile. All statistical analyses were performed by an independent medical statistician (K.M.) using SPSS Statistics version 23 (IBM, Tokyo, Japan).

We conducted univariate analysis by Kaplan-Meier analysis with the Breslow test to compare the equality of survival curves for individual variables for demographic, clinical, laboratory, imaging and autoantibody parameters at diagnosis. Variables with available data for fewer than 350 cases were excluded from analysis. All continuous variables were converted to dichotomous variables for analysis, and cut-off values were determined by receiver-operating characteristics [26]. Multiple dichotomous variables were used for diagnosis (PM, classic DM or CADM) or MSAs (anti-MDA5$^-$/anti-ARS$^-$, anti-MDA5$^+$/anti-ARS$^-$, anti-MDA5$^-$/anti-ARS$^+$ or anti-MDA5$^+$/anti-ARS$^+$).

The cause-specific Cox proportional hazards model was used for multivariate analysis to identify an optimal model for predicting poor survival caused by respiratory insufficiency. In some cases, we applied subdistribution hazards model, and/or imputed all missing values of dichotomous variables using a multiple imputation method and resultant generation of 1000 multiple imputation data sets, to verify the original model. During the stepwise selection process, sex, age at diagnosis and anti-MDA5 and anti-ARS antibodies were first adopted into the model, and all other variables at the time of diagnosis with $P < 0.2$ in the univariate analysis were subsequently entered into the model as potential predictors. Backward deletion ($P \geqslant 0.15$) and forward inclusion ($P < 0.1$) were performed using the likelihood test to select the predictor variables in the model. Finally, selected induction treatment drugs were included in the final multivariate model as potential confounders. The results were shown as the hazard ratio (HR) with a 95% CI.

Results

Baseline characteristics

Of 499 patients registered, 2 were excluded because of incomplete data during the follow-up period, and 497 incident cases were enrolled in the study. The baseline characteristics of the cohort (available data $\geqslant$350) are shown in Table 1. The disease duration at diagnosis was 3 months (2.5–97.5 percentile 1–62), indicating that most patients were diagnosed and treated at an early stage. Our cohort consisted mainly of classic DM and CADM; only 15% were classified as PM. Muscle weakness was detected in 48%. Chest HRCT findings were available for 496 patients: a lower consolidation/GGA pattern was most prevalent, followed by lower reticulation and random GGA patterns. There were 166 patients (34%) with anti-ARS antibodies; 44 with anti-Jo-1, 41 with anti-EJ, 13 with anti-OJ, 32 with anti-PL-7, 26 with anti-PL-12 and 12 with anti-KS. Two patients had two anti-ARS specificities simultaneously: one was positive for anti-Jo-1 and anti-EJ, and the other for anti-Jo-1 and anti-PL-7. Anti-MDA5 was detected in 209 patients (42%). Although anti-ARS and anti-MDA5 antibodies were mutually exclusive in general, two patients had both (anti-PL-7 or anti-KS in one each). The detailed clinical course of one such patient is published elsewhere [27].

Table 1 Baseline characteristics and initial treatment for 497 patients with PM/DM-associated ILD in the JAMI database

Variables	Value	Available data per outcome
Demographics		
Age at onset, years	57 (29–80)	497 (100)
Male	167 (34)	497 (100)
Body weight, kg	55 (39–85)	492 (99)
Disease duration at diagnosis, month	3 (1–62)	495 (100)
Diagnosis		
PM	76 (15)	497 (100)
Classic DM	158 (32)	
CADM	263 (53)	
Clinical features		
Fever	237 (49)	482 (97)
Raynaud's phenomenon	69 (16)	443 (89)
Muscle weakness	233 (48)	486 (98)
Neck V-sign	92 (21)	443 (89)
Skin ulceration	48 (10)	459 (92)
Periungual erythema	260 (58)	452 (91)
Laboratory parameters		
CRP, mg/dl	0.7 (0.0–13.4)	486 (98)
CK, IU/l	202 (32–4267)	486 (98)
Aldolase, IU/l	9.0 (3.6–91.2)	424 (85)
KL-6, U/ml	801 (208–4431)	476 (96)
SP-D, ng/ml	91 (16–615)	380 (76)
Ferritin, ng/ml	357 (22–3846)	361 (73)
Chest HRCT patterns		
Lower consolidation/GGA	268 (54)	496 (100)
Lower reticulation	167 (34)	
Random GGA	60 (12)	
SpO_2, %	96 (89–99)	477 (96)
MSAs		
Anti-ARS$^-$/anti-MDA5$^-$	122 (25)	493 (99)
Anti-ARS$^+$/anti-MDA5$^-$	162 (33)	
Anti-ARS$^-$/anti-MDA5$^+$	200 (41)	
Anti-ARS$^+$/anti-MDA5$^+$	2 (0)	
Drugs used for induction treatment		
Any CS	485 (98)	497 (100)
High-dose CS	289 (58)	497 (100)
Initial dose of CS (PSL equivalent), mg/day	50 (1.8–100)	497 (100)
CS pulse therapy	285 (57)	497 (100)
CYC	223 (45)	497 (100)
Intravenous CYC	218 (44)	497 (100)
CSA	238 (48)	497 (100)
Tac	226 (45)	497 (100)
MTX	17 (3)	497 (100)
AZA	21 (4)	497 (100)
MMF	6 (1)	497 (100)
IVIG	86 (17)	497 (100)
Rituximab	5 (1)	497 (100)
PMX-DHP	47 (9)	497 (100)
Initial treatment regimens		
High-dose CS alone	30 (6)	497 (100)
High-dose CS + CYC	5 (1)	497 (100)
High-dose CS + CSA/Tac	110 (22)	497 (100)
High-dose CS + CYC + CSA/Tac	145 (29)	497 (100)

Values listed as *n* (%); continuous variables are shown as median (2.5–97.5 percentile). CADM: clinically amyopathic DM; CK: creatine kinase; KL-6: Krebs von den Lungen-6; SP-D: surfactant protein D; HRCT: high-resolution CT; GGA: ground glass attenuation; MSA: myositis-specific autoantibody; ARS: aminoacyl tRNA synthetase; MDA5: melanoma differentiation-associated gene 5; PSL: prednisolone; Tac: tacrolimus; PMX-DHP: polymyxin B-immobilized fibre column-direct haemoperfusion; JAMI: Multicentre Retrospective Cohort of Japanese Patients with Myositis-associated ILD; ILD: interstitial lung disease.

Induction treatment regimens

As shown Table 1, almost all of the patients were treated with CS: 58% with high-dose CS and 57% with CS pulse therapy. Calcineurin inhibitor (CSA or tacrolimus) was preferably used (80%) as an immunosuppressant, rather than CYC, MTX, AZA or MMF. In regimens using CYC, it was almost always administered intravenously every 2–4 weeks. Patients were frequently treated with a combination of high-dose CS with immunosuppressants: 'double combo' with CYC in 5 (1%), 'double combo' with calcineurin inhibitor in 110 (22%), and 'triple combo' with CYC and calcineurin inhibitor in 145 (29%). IVIG was administered to 86 patients (17%), while MMF and rituximab was rarely used. Notably, 47 patients (9%) underwent polymyxin B-immobilized fibre column-direct haemoperfusion [28].

Patient outcomes

The median observation period was 20 months (2.5–97.5 percentile 1–50), during which 93 patients died. The cause of death was respiratory insufficiency directly related to PM/DM-associated ILD in 76 (82%), infection in 5 (5%), malignancy in 5 (5%), and other causes such as renal insufficiency, cardiomyopathy and suicide in 7 (8%). Thus, the majority of deaths in the JAMI cohort were directly due to ILD.

Initial predictors of mortality due to ILD

We examined initial predictors at the time of diagnosis of mortality directly due to ILD by univariate analysis of all initial variables (excluding induction treatment regimens) with available data for 350 or more cases. Table 2 lists initial parameters significantly associated with ILD mortality. The following initial parameters were identified as predictors for poor ILD outcomes: male, older age at disease onset (⩾60 years), CADM, classic DM, fever, neck V-sign, skin ulceration, periungual erythema, higher CRP (⩾1 mg/dl), higher KL-6 (⩾1000 U/ml), higher ferritin (⩾500 ng/ml), lower consolidation/GGA and random GGA patterns on chest HRCT, lower SpO_2 (<95%) and anti-MDA5

Table 2 Initial parameters significantly associated with mortality due to ILD, identified by univariate analysis

Variable	*N* (%)		*P*-value
	Dead (*n* = 76[a])	Alive (*n* = 421[a])	
Demographics			
Male	32 (42)	135 (32)	0.044
Age at onset ⩾60 years	53 (70)	167 (40)	<0.001
Diagnosis			
PM	2 (3)	74 (18)	Reference
CADM	61 (80)	202 (48)	<0.001[b]
Classic DM	13 (17)	145 (34)	0.009[b]
Clinical features			
Fever	59 (77)	178 (44)	<0.001
Raynaud's phenomenon	3 (5)	66 (17)	0.012
Muscle weakness	23 (33)	210 (51)	0.014
Neck V-sign	19 (29)	73 (19)	0.045
Skin ulceration	12 (17)	36 (9)	0.024
Periungual erythema	48 (69)	212 (56)	0.046
Laboratory parameters			
CRP ⩾1 mg/dl	55 (72)	154 (38)	<0.001
CK <750 IU/l	68 (90)	293 (72)	0.001
Aldolase <17.5 IU/l	62 (94)	243 (68)	<0.001
KL-6 ⩾1000 U/ml	40 (53)	141 (35)	0.007
SP-D <100 ng/ml	50 (74)	154 (49)	<0.001
Ferritin ⩾500 ng/ml	43 (74)	95 (31)	<0.001
Chest HRCT patterns			
Lower consolidation/GGA	50 (66)	218 (52)	0.027
Lower reticulation	13 (17)	154 (37)	0.001
Random GGA	17 (22)	43 (10)	0.005
SpO_2 <95%	38 (50)	78 (20)	<0.001
MSAs			
Anti-ARS$^-$/anti-MDA5$^-$	5 (7)	117 (28)	Reference
Anti-ARS$^+$/anti-MDA5$^-$	4 (5)	160 (39)	<0.001[b]
Anti-ARS$^-$/anti-MDA5$^+$	64 (88)	138 (33)	<0.001[b]

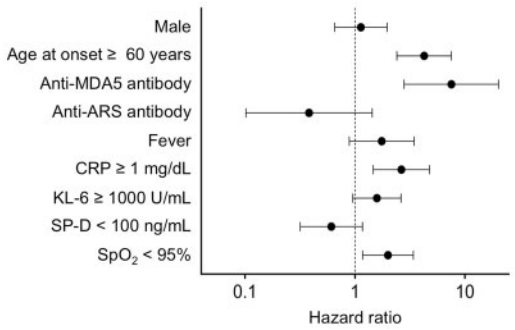
P-values were calculated using the Breslow test. [a]Maximum number of subjects per outcome. [b]Compared with the reference. CADM: clinically amyopathic DM; CK creatine kinase; KL-6: Krebs von den Lungen-6; SP-D: surfactant protein D; HRCT: high-resolution CT; GGA: ground glass attenuation; MSA: myositis-specific autoantibody; ARS: aminoacyl tRNA synthetase; MDA5: melanoma differentiation-associated gene 5; ILD: interstitial lung disease.

antibody. In contrast, favourable ILD outcomes were associated with Raynaud's phenomenon, muscle weakness, higher creatine kinase, higher aldolase, higher SP-D and anti-ARS antibody. It was of note that the majority of predictors for ILD outcomes identified in univariate analysis were associated with anti-MDA5 antibody (supplementary Table S1, available at *Rheumatology* online).

To generate an appropriate predictive model for mortality due to PM/DM-associated ILD, we conducted multivariate analysis using a stepwise selection of parameters and the cause-specific Cox proportional hazards regression model to identify independent predictors. Sex, age at diagnosis, anti-MDA5 antibody and anti-ARS antibody were first adopted into the model, since demographic features and MSAs are reported as a poor survival factor in most previous studies [9–19]. Subsequently, all other initial variables with $P < 0.2$ in the univariate analysis were sequentially included in the model, and the number of variables was reduced by repeating the step-up and step-down procedure. Fig. 1 shows a final predictive model of mortality derived from 349 patients in whom all variable data were available, consisting of nine independent variables. In particular, age at disease onset $\geqslant$60 years (HR = 4.3, 95% CI: 2.4, 7.5; $P < 0.001$), anti-MDA5 antibody (HR = 7.5, 95% CI: 2.8, 20.2; $P < 0.001$), CRP $\geqslant$1 mg/dl (HR = 2.6, 95% CI: 1.5, 4.8; $P = 0.001$) and SpO_2 <95% (HR = 2.0, 95% CI: 1.2, 3.4; $P = 0.011$) were selected as independent risks for ILD mortality. The identical variables were selected when subdistribution hazards model was applied (supplementary Table S2, available at *Rheumatology* online).

When we included the drugs used for induction treatment (including high-dose CS, the calcineurin inhibitors CSA or tacrolimus, CYC and IVIG) in the final multivariate model as potential confounders, the four independent risk factors remained statistically significant: age at onset (HR = 3.8, 95% CI: 2.2, 6.7; $P < 0.001$), anti-MDA5 antibody (HR = 6.5, 95% CI: 2.3, 17.9; $P < 0.001$), CRP (HR = 2.6, 95% CI: 1.5, 4.7; $P = 0.001$) and SpO_2 (HR = 2.1, 95% CI: 1.2, 3.5; $P = 0.005$), while KL-6 $\geqslant$1000 U/ml was additionally selected as an independent risk factor (HR = 2.0, 95% CI: 1.2, 3.3; $P = 0.01$).

Fig. 1 Predictive model for mortality due to respiratory insufficiency in patients with PM/DM-associated ILD



Initial predictors of poor prognosis due to fatal respiratory insufficiency were identified by multivariate analysis using a stepwise selection of parameters and the cause-specific Cox proportional hazards regression model. The hazard ratio with 95% CI is shown for each variable finally selected. ILD: interstitial lung disease; KL-6: Krebs von den Lungen-6; SP-D: surfactant protein; ARS: aminoacyl; MDA5: melanoma differentiation-associated gene 5.

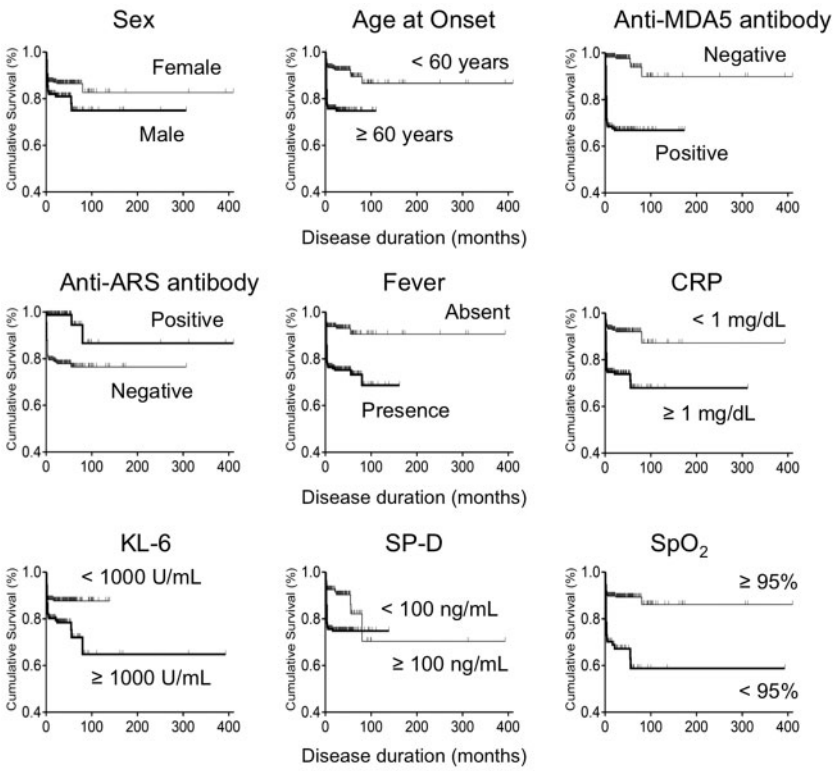
Fig. 2 shows Kaplan-Meier analyses comparing the equality of cumulative survival curves between two groups stratified by individual prognostic factors. The cumulative survival rates were significantly different ($P < 0.01$ for all comparisons), and this difference was apparent even early in the course of the disease because of deaths due to RP-ILD. The survival curves for the low and high SP-D groups intersected at 80 months, indicating possible violation in proportional hazards model. Exclusion of SP-D from the explanatory variables resulted in the selection of age at onset, anti-MDA5 antibody and CRP as variables for ILD mortality (supplementary Fig. S1, available at *Rheumatology* online). Since there were several missing variables in our database, a multiple imputation method was applied to confirm the model validity (supplementary Fig. S2, available at *Rheumatology* online). The significant variables obtained were principally identical, and included age at disease onset, anti-MDA5 antibody, CRP, KL-6 and SpO_2.

Because 67 (88%) deaths occurred in anti-MDA5-positive patients, our model was likely to depend heavily on the anti-MDA5 antibody. To assess this possibility, we generated predictive models for the mortality, separately in patients with and without anti-MDA5 antibody. Two patients with coexisting anti-MDA5 and anti-ARS antibodies were included in the anti-MDA5-positive group. As shown in supplementary Table S3, available at *Rheumatology* online, and Fig. 3A, in anti-MDA5-positive patients, age at disease onset $\geqslant$60 years and CRP $\geqslant$1 mg/dl were again significant explanatory variables for ILD mortality risk, while periungual erythema was identified as a favourable predictor. The same variables were selected when a multiple imputation method was applied (supplementary Fig. S3A, available at *Rheumatology* online). In contrast, no significant explanatory variable for ILD mortality risk was identified in anti-MDA5-negative patients, regardless of the absence (supplementary Table S4, available at *Rheumatology* online; Fig. 3B) or the presence of a multiple imputation method (supplementary Fig. S3B, available at *Rheumatology* online), but there were trends toward a correlation between ILD mortality risk and age at disease onset $\geqslant$60 years or CRP $\geqslant$1 mg/dl.

Discussion

In this study, we used the large-scale JAMI database to identify initial predictors for mortality due to respiratory insufficiency in adult patients with PM/DM-associated ILD. A number of factors at diagnosis were selected by univariate analysis, but cause-specific Cox proportional hazards models revealed the following to be predictors independently associated with future poor mortality due

Fig. 2 Cumulative survival rates between groups stratified by independent predictors of ILD mortality



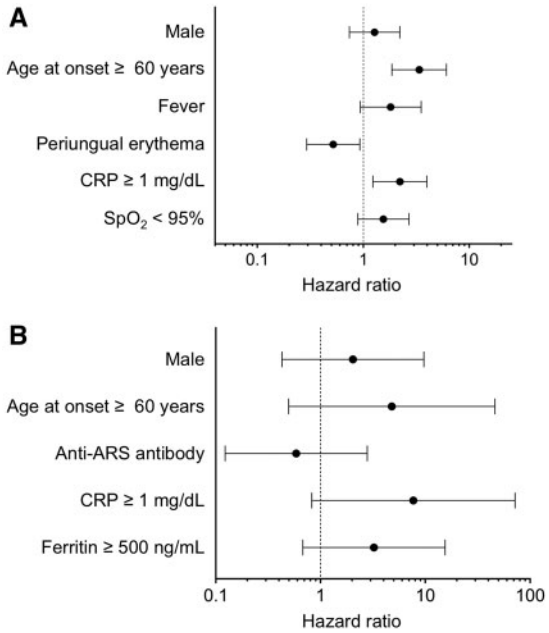
Kaplan-Meier analysis with the Breslow test was used for factors selected by final model for predictors for ILD mortality. Censors were indicated in each graph. ILD: interstitial lung disease; KL-6: Krebs von den Lungen-6; SP-D: surfactant protein; ARS: aminoacyl; MDA5: melanoma differentiation-associated gene 5.

to ILD: age at disease onset, anti-MDA5 antibody, CRP and SpO_2. This final model was verified by a variety of different models. Since age, CRP and SpO_2 are readily available in routine clinical practice, and kits to measure the anti-MDA5 antibody are now commercially available [29, 30], our findings are widely applicable for identifying PM/DM patients with intractable ILD who require intensive treatment at an early stage. Our results will also assist in designing appropriate patient inclusion criteria for future clinical trials for PM/DM-associated ILD.

JAMI is a nationwide, large-scale cohort established in Japan. It is the first multicentre cohort focusing on PM/DM-associated ILD, although there are several multicentre cohorts of patients with idiopathic inflammatory myopathy [31, 32], juvenile-onset myositis [33] and anti-synthetase syndrome [34, 35]. The patient population might vary between specialties, because the clinical presentation of PM/DM is quite heterogeneous; patients with progressive or advanced ILD with significant respiratory distress are likely to be referred to pulmonologists or critical care physicians, while those whose predominant symptom is skin rashes are often referred to dermatologists. Therefore, patients in the JAMI cohort are cared for by a wide variety of specialties to avoid potential patient selection bias. Finally, because serum samples obtained at the time of diagnosis were available for all patients, we were able to run assays for a full panel of MSAs. These features give the JAMI cohort several advantages for analysing various clinical aspects of PM/DM-associated ILD.

This study confirmed many prognostic factors reported in previous studies, including gender, age at disease onset, CADM, classic DM, fever, skin ulceration, periungual erythema, muscle weakness, creatine kinase, ferritin, chest HRCT patterns, SpO_2, anti-MDA5 antibody and anti-ARS antibody, although the populations and endpoints were somewhat different among studies [9–19]. Since many of these factors are correlated with each other, it is difficult to identify primary contributing factors from previous studies, primarily because of small sample sizes. In fact, in our cohort, the majority of these factors were not selected as independent predictors in multivariate analysis. Our predictive modelling successfully identified age at disease onset, CRP and anti-MDA5 antibody as independent initial predictors of poor ILD prognosis. In particular, anti-MDA5 antibody provided the highest HR, with a 7.5-fold increase in risk. In fact, the other prognostic factors were associated with anti-MDA5 antibody, and were mostly relevant to anti-MDA5-positive patients who dominated the analysis, since we failed to identify risk for ILD mortality in patients without anti-MDA5 antibody, probably because of the small number of deaths. This finding is consistent with a meta-analysis of 13 studies that found a pooled sensitivity

Fig. 3 Predictive models for mortality due to respiratory insufficiency in patients with and without anti-MDA5 antibody



Initial predictors of poor prognosis due to fatal respiratory insufficiency were identified in patients with anti-MDA5 antibody (**A**) and in those without anti-MDA5 antibody (**B**), by multivariate analysis using a stepwise selection of parameters and the cause-specific Cox proportional hazards regression model. The hazard ratio with 95% CI is shown for each variable finally selected. ILD: interstitial lung disease; MDA5: melanoma differentiation-associated gene 5; ARS: aminoacyl.

and specificity of anti-MDA5 antibody for RP-ILD of 77 and 86%, respectively, in DM patients [36].

In contrast, we found that anti-ARS antibody tended to predict favourable ILD outcomes, at least in the short term, although this is likely a reflection of the strong association between anti-MDA5 antibody and poor prognosis. In this regard, a previous study found no significant increase in mortality in patients with anti-synthetase syndrome compared with the general US population [37]. In addition, Yoshida *et al.* [38] reported that the anti-MDA5 antibody is associated with a higher 3-month mortality compared with the anti-ARS antibody. Thus, MSA measurement at diagnosis is highly useful for predicting treatment responses and outcomes in patients with PM/DM-associated ILD.

The prognostic significance of CRP in patients with PM/DM-associated ILD has not been emphasized in the literature, although a recent meta-analysis indicated that CRP is associated with an increased risk of developing ILD in PM/DM patients [39]. Notably, in a small Chinese study of 40 patients with CADM, multivariate logistic regression analysis showed that anti-MDA5 antibody combined with elevated CRP is an independent risk factor for developing RP-ILD [15]. Interestingly, CRP is a prognostic factor for other forms of ILD, such as biopsy-proven idiopathic pulmonary fibrosis [40] and SS-associated ILD [41], suggesting that this biomarker might reflect inflammation in the lung parenchyma that leads to irreversible damage.

Since JAMI is a retrospective cohort, management was determined by attending physicians, who were unaware of the MSA data. In addition, the treatment regimens for the JAMI cohort were considerably different from those in previous reports. The JAMI patients were often treated with calcineurin inhibitors and a 'triple combo' consisting of high-dose CS, CYC and calcineurin inhibitor. IVIG and polymyxin B-immobilized fibre column-direct haemoperfusion were occasionally administered on top of immunosuppressive regimens [42, 43]. MMF or rituximab was seldom used, potentially contributing to worse survivals in our cohort. The selections of treatment regimens are different from those in other countries, primarily due to Japan's unique health insurance system. Although these treatment regimens had the potential to influence patient outcomes, our multivariate model consistently selected the same independent prognostic factors even after adjusting for the drugs used in induction treatment as potential confounders.

The present study has potential limitations due to its retrospective nature. Patients were selected mainly from tertiary referral hospitals, so there may be a bias toward more severe forms of the disease. However, the nature of a multicentre study and the inclusion of dermatology centres may minimize this bias. In addition, because the observation period after diagnosis was a median of 20 months, our current analysis only detected predictors for short-term mortality. This feature might have caused us to overestimate the importance of the anti-MDA5 antibody due to its strong association with RP-ILD. Long-term outcomes can be assessed as more follow-up data become available. Finally, information on smoking was not included in the JAMI database, because it has never been reported as a poor prognostic factor in patients with PM/DM-associated ILD. However, a recent multicentre registry of patients with idiopathic inflammatory myopathy (EuroMyositis) found an association of smoking with ILD [31], urging us to examine a potential influence of smoking habits on ILD prognosis in the JAMI cohort as a future project.

In conclusion, we successfully generated a model to predict ILD mortality in patients with PM/DM-associated ILD at diagnosis, based on a newly established multicentre cohort. Our findings are easily applied to routine care, and may help to identify patients who are at high risk for ILD mortality and require immediate intensive treatment.

Acknowledgements

Other JAMI investigators: Yutaka Okano (Kawasaki Municipal Kawasaki Hospital), Yukie Yamaguchi (Yokohama City University Graduate School of Medicine), Yoshinori Taniguchi (Kochi Medical School Hospital, Kochi University), Jun Kikuchi (Saitama Medical Centre, Saitama Medical University), Makoto

Kubo (Yamaguchi University Graduate School of Medicine), Masaki Watanabe (Graduate School of Medical and Dental Sciences, Kagoshima University), Tatsuhiko Harada (Nagasaki University School of Medicine), Taisuke Kazuyori (The Jikei University School of Medicine Katsushika Medical Centre), Hideto Kameda (Toho University Ohashi Medical Centre), Makoto Kaburaki (Toho University School of Medicine), Yasuo Matsuzawa (Toho University Medical Centre, Sakura Hospital), Shunji Yoshida (Fujita Health University School of Medicine), Yasuko Yoshioka, Takuya Hirai (Juntendo University Urayasu Hospital), Yoko Wada (Niigata University Graduate School of Medical and Dental Sciences), Koji Ishii, Sakuhei Fujiwara (Faculty of Medicine Oita University), Takeshi Saraya (Kyorin University), Kozo Morimoto (Fukujuji Hospital, Japan Anti-Tuberculosis Association), Tetsu Hara (Hiratsuka Kyosai Hospital), Hiroki Suzuki (Saiseikai Yamagata Saisei Hospital), Hideki Shibuya (Tokyo Teishin Hospital), Yoshinao Muro (Nagoya University Graduate School of Medicine), Ryoichi Aki (Kitasato University School of Medicine), Takuo Shibayama (National Hospital Organisation Okayama Medical Centre), Shiro Ohshima (National Hospital Organisation Osaka Minami Medical Centre), Yuko Yasuda (Saiseikai Kumamoto Hospital), Masaki Terada (Saiseikai Niigata Daini Hospital) and Yoshie Kawahara (Keiyu Hospital). Author contributions: conceived and designed the study: S.S., K.M., N.N., T.G., M.K.; analysed the data: K.M.; contributed data collection/analysis tools: S.S., K.M., N.N., Y.Kawaguchi, A.K., M.T., K.I., T.Nunokawa, Y.T., K.A., Y.Kaneko, T.G., T.U., S.K., T.Naniwa, M.K. and JAMI investigators; wrote the paper: S.S., K.M., N.N., Y.Kawaguchi, A.K., M.T., K.I., T.Nunokawa, Y.T., K.A., Y.Kaneko, T.G., T.U., S.K., T.Naniwa, M.K. and JAMI investigators.

Funding: This work was supported by a research grant from Astellas and a research grant for intractable diseases from the Japanese Ministry of Health, Labour and Welfare. The funders had no role in the study design, data collection and analysis, decision to publish or preparation of the manuscript.

Disclosure statement: S.S. and M.K. hold a patent for the anti-MDA5 antibody measurement kit. The other authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* online.

References

1 Tieu J, Lundberg IE, Limaye V. Idiopathic inflammatory myositis. Best Pract Res Clin Rheumatol 2016;30:149–68.

2 Johnson C, Pinal-Fernandez I, Parikh R *et al*. Assessment of mortality in autoimmune myositis with and without associated interstitial lung disease. Lung 2016;194:733–7.

3 Mimori T, Nakashima R, Hosono Y. Interstitial lung disease in myositis: clinical subsets, biomarkers, and treatment. Curr Rheumatol Rep 2012;14:264–74.

4 Morisset J, Johnson C, Rich E, Collard HR, Lee JS. Management of myositis-related interstitial lung disease. Chest 2016;150:1118–28.

5 Hamaguchi Y, Kuwana M, Hoshino K *et al*. Clinical correlations with dermatomyositis-specific autoantibodies in adult Japanese patients with dermatomyositis: a multicenter cross-sectional study. Arch Dermatol 2011;147:391–8.

6 Moghadam-Kia S, Oddis CV, Sato S, Kuwana M, Aggarwal R. Anti-melanoma differentiation-associated gene 5 is associated with rapidly progressive lung disease and poor survival in US patients with amyopathic and myopathic dermatomyositis. Arthritis Care Res 2016;68:689–94.

7 Kotani T, Makino S, Takeuchi T *et al*. Early intervention with corticosteroids and cyclosporin A and 2-hour postdose blood concentration monitoring improves the prognosis of acute/subacute interstitial pneumonia in dermatomyositis. J Rheumatol 2008;35:254–9.

8 Horai Y, Isomoto E, Koga T *et al*. Early diagnosis and treatment for remission of clinically amyopathic dermatomyositis complicated by rapid progress interstitial lung disease: a report of two cases. Mod Rheumatol 2013;23:190–4.

9 Takada T, Suzuki E, Nakano M *et al*. Clinical features of polymyositis/dermatomyositis with steroid-resistant interstitial lung disease. Intern Med 1998;37:669–73.

10 Selva-O'Callaghan A, Labrador-Horrillo M, Muñoz-Gall X *et al*. Polymyositis/dermatomyositis-associated lung disease: analysis of a series of 81 patients. Lupus 2005;14:534–42.

11 Cao H, Xia Q, Pan M *et al*. Gottron papules and Gottron sign with ulceration: a distinctive cutaneous feature in a subset of patients with classic dermatomyositis and clinically amyopathic dermatomyositis. J Rheumatol 2016;43:1735–42.

12 Sato S, Hirakata M, Kuwana M *et al*. Autoantibodies to a 140-kd polypeptide, CADM-140, in Japanese patients with clinically amyopathic dermatomyositis. Arthritis Rheum 2005;52:1571–6.

13 Gono T, Kuwana M. Choosing the right biomarkers to predict ILD in myositis. Nat Rev Rheumatol 2016;12:504–6.

14 Gono T, Kawaguchi Y, Satoh T *et al*. Clinical manifestation and prognostic factor in anti-melanoma differentiation-associated gene 5 antibody-associated interstitial lung disease as a complication of dermatomyositis. Rheumatology (Oxford) 2010;49:1713–9.

15 Xu Y, Yang CS, Li YJ *et al*. Predictive factors of rapidly progressive-interstitial lung disease in patients with clinically amyopathic dermatomyositis. Clin Rheumatol 2016;35:113–6.

16 Hozumi H, Fujisawa T, Nakashima R *et al*. Comprehensive assessment of myositis-specific autoantibodies in polymyositis/dermatomyositis-associated interstitial lung disease. Respir Med 2016;121:91–9.

17 Koga T, Fujikawa K, Horai Y *et al*. The diagnostic utility of anti-melanoma differentiation-associated gene 5 antibody testing for predicting the prognosis of Japanese patients with DM. Rheumatology (Oxford) 2012;51:1278–84.

18 Tanizawa K, Handa T, Nakashima R *et al*. The prognostic value of HRCT in myositis-associated interstitial lung disease. Respir Med 2013;107:745–52.

19 Fujiki Y, Kotani T, Isoda K *et al*. Evaluation of clinical prognostic factors for interstitial pneumonia in anti-MDA5 antibody-positive dermatomyositis patients. Mod Rheumatol 2017;11:1–8.

20 Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med 1975;292:344–7.

21 Sontheimer RD. Would a new name hasten the acceptance of amyopathic dermatomyositis (dermatomyositis siné myositis) as a distinctive subset within the idiopathic inflammatory dermatomyopathies spectrum of clinical illness? J Am Acad Dermatol 2002;46:626–36.

22 American Thoracic Society, European Respiratory Society. American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 2002;165:277–304.

23 Tanizawa K, Handa T, Nakashima R *et al*. HRCT features of interstitial lung disease in dermatomyositis with anti-CADM-140 antibody. Respir Med 2011;105:1380e7.

24 Forman MS, Nakamura M, Mimori T, Gelpi C, Hardin JA. Detection of antibodies to small nuclear ribonucleoproteins and small cytoplasmic ribonucleoproteins using unlabeled cell extracts. Arthritis Rheum 1985;28:1356–61.

25 Sato S, Hoshino K, Satoh T *et al*. RNA helicase encoded by melanoma differentiation-associated gene 5 is a major autoantigen in patients with clinically amyopathic dermatomyositis: association with rapidly progressive interstitial lung disease. Arthritis Rheum 2009;60:2193–200.

26 Zweig MH, Campbell G. Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine. Clin Chem 1993;39:561–77.

27 Naniwa T, Tamechika S, Okazaki Y, Maeda S, Kuwana M. Coexistence of anti-melanoma differentiation-associated gene 5 and anti-aminoacyl-transfer RNA synthetase antibodies in a patient with dermatomyositis and rapidly progressive and relapsing interstitial lung disease. Mod Rheumatol Case Rep 2017;1:3–8.

28 Abe S, Azuma A, Mukae H *et al*. Polymyxin B-immobilized fiber column (PMX) treatment for idiopathic pulmonary fibrosis with acute exacerbation: a multicenter retrospective analysis. Intern Med 2012;51:1487–91.

29 Sato S, Murakami A, Kuwajima A *et al*. Clinical utility of an enzyme-linked immunosorbent assay for detecting anti-melanoma differentiation-associated gene 5 autoantibodies. PLoS One 2016;11:e0154285.

30 Cavazzana I, Fredi M, Ceribelli A *et al*. Testing for myositis specific autoantibodies: comparison between line blot and immunoprecipitation assays in 57 myositis sera. J Immunol Methods 2016;433:1–5.

31 Lilleker JB, Vencovsky J, Wang G *et al*. The EuroMyositis registry: an international collaborative tool to facilitate myositis research. Ann Rheum Dis 2018;77:30–9.

32 Nuño-Nuño L, Joven BE, Carreira PE *et al*. Mortality and prognostic factors in idiopathic inflammatory myositis: a retrospective analysis of a large multicenter cohort of Spain. Rheumatol Int 2017;37:1853–61.

33 Martin N, Krol P, Smith S *et al*. A national registry for juvenile dermatomyositis and other paediatric idiopathic inflammatory myopathies: 10 years' experience; the Juvenile Dermatomyositis National (UK and Ireland) Cohort Biomarker Study and Repository for Idiopathic Inflammatory Myopathies. Rheumatology (Oxford) 2011;50:137–45.

34 Cavagna L, Nuño L, Scirè CA *et al*. Clinical spectrum time course in anti Jo-1 positive antisynthetase syndrome: results from an international retrospective multicenter study. Medicine 2015;94:e1144.

35 Trallero-Araguás E, Grau-Junyent JM, Labirua-Iturburu A *et al*. Clinical manifestations and long-term outcome of anti-Jo1 antisynthetase patients in a large cohort of Spanish patients from the GEAS-IIM group. Semin Arthritis Rheum 2016;46:225–31.

36 Chen Z, Cao M, Plana MN *et al*. Utility of anti-melanoma differentiation-associated gene 5 antibody measurement in identifying patients with dermatomyositis and a high risk for developing rapidly progressive interstitial lung disease: a review of the literature and a meta-analysis. Arthritis Care Res 2013;65:1316–24.

37 Pinal-Fernandez I, Casal-Dominguez M, Huapaya JA *et al*. 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 (Oxford) 2017;56:999–1007.

38 Yoshida N, Okamoto M, Kaieda S *et al*. Association of anti-aminoacyl-transfer RNA synthetase antibody and anti-melanoma differentiation-associated gene 5 antibody with the therapeutic response of polymyositis/dermatomyositis-associated interstitial lung disease. Respir Investig 2017;55:24–32.

39 Zhang L, Wu G, Gao D *et al*. Factors associated with interstitial lung disease in patients with polymyositis and dermatomyositis: a systematic review and meta-analysis. PLoS One 2016;11:e0155381.

40 Lee SH, Shim HS, Cho SH *et al*. Prognostic factors for idiopathic pulmonary fibrosis: clinical, physiologic, pathologic, and molecular aspects. Sarcoidosis Vasc Diffuse Lung Dis 2011;28:102–12.

41 Liu X, Mayes MD, Pedroza C *et al*. Does C-reactive protein predict the long-term progression of interstitial lung disease and survival in patients with early systemic sclerosis? Arthritis Care Res 2013;65:1375–80.

42 Suzuki Y, Hayakawa H, Miwa S *et al*. Intravenous immunoglobulin therapy for refractory interstitial lung disease associated with polymyositis/dermatomyositis. Lung 2009;187:201–6.

43 Teruya A, Kawamura K, Ichikado K *et al*. Successful polymyxin B hemoperfusion treatment associated with serial reduction of serum anti-CADM-140/MDA5 antibody levels in rapidly progressive interstitial lung disease with amyopathic dermatomyositis. Chest 2013;144:1934–6.