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Original Article

A clinical analysis of prognostic factors for dermatomyositis-associated interstitial lung disease

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Abstract: Objective: Interstitial lung disease (ILD) is a common and life-threatening manifestation of dermatomyositis (DM). However, little is known about the factors that influence the prognosis of DM-ILD. The present study aimed to evaluate the characteristics and outcomes of ILD in DM and to determine the prognostic factors of DM-ILD. Methods: A retrospective analysis of DM-ILD was performed by survival analysis. Clinical manifestations and laboratory data were analyzed. The ILD-associated survival rates were estimated by using the Kaplan-Meier method to identify potential prognostic factors. Factors with *P* values ≤ 0.10 were subjected to a multivariate Cox regression analysis. *P* values ≤ 0.05 were considered statistically significant. Results: Overall, 103 DM patients with ILD were enrolled in the study. The mean follow-up period was 21.9 months (range, 2-120 months). The clinical presentation of ILD was the acute/subacute form in 48 patients (46.6%) and the chronic form in 55 patients (48.2%). ILD-associated mortality was 34.9%. The statistical analysis suggested that age over 60 years, the acute/subacute form of ILD, heliotrope sign, ESR>20 mm/h, CRP>10 mg/L and hypocalcemia are independent predictors of poor outcomes in DM-ILD. Moreover, negative correlations between serum calcium and the levels of CRP and ESR were found in DM-ILD. Conclusions: Age over 60 years, the acute/subacute form of ILD, heliotrope sign, ESR>20 mm/h, CRP>10 mg/L and hypocalcemia predict poor outcomes in DM-ILD patients. The serum calcium level may be an inflammatory biomarker in DM-ILD patients.

Keywords: Dermatomyositis, interstitial lung disease

Introduction

Dermatomyositis (DM) is a systemic inflammatory disease that is characterized by proximal muscle weakness and other organ involvement, especially the lungs [1, 2]. Pulmonary manifestations in DM include respiratory muscle weakness, aspiration pneumonia, infection- and drug-induced pneumonia and interstitial lung disease (ILD) [3, 4]. Previous studies have shown that ILD, with a prevalence of 20-65%, is considered a common cause of morbidity in DM [4, 5]. Therefore, determining the prognostic factors for ILD is crucial for managing patients with DM.

Few reports regarding the prognostic factors for myositis-associated ILD are available [6-8]. However, there are some variations in the clinical course and pathogenesis among cases of myositis-associated ILD [9, 10]. The present study focused on DM-ILD patients after excluding PM, cancer-associated DM and clinically amyopathic dermatomyositis (CADM). The aims of this retrospective study were to evaluate the clinical characteristics and outcomes and to determine the prognostic factors of 103 patients with DM-ILD in a large series of patients from two centers.

Materials and methods

Patient selection

This retrospective study included patients with a diagnosis of DM from January 2001 to January 2016 in ChangZheng hospital and Changhai hospital, which are both tertiary teaching medi-

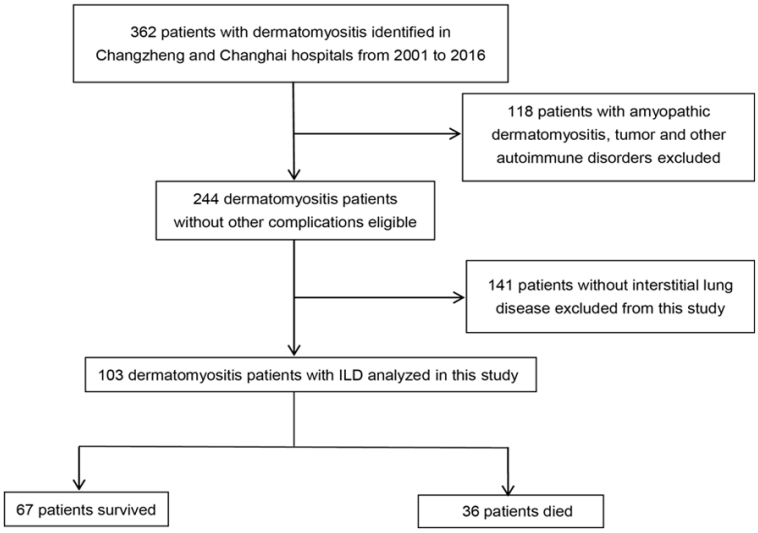

Figure 1. Patient flow diagram.

cal centers in China. The diagnosis of DM was based on the Bohan and Peter criteria [11], including symmetric muscle weakness, increased serum muscle enzymes, myopathic changes on electromyography, typical histologic findings on muscle biopsy, and characteristic dermatologic manifestations. During the study period, 362 consecutive DM patients were reviewed. Among the 362 DM patients, 103 DM with ILD patients were identified after excluding 40 patients with amyopathic dermatomyositis (ADM), 46 patients with cancer-associated DM, 32 DM patients with other connective tissue disorders and 141 DM patients without ILD (**Figure 1**). This retrospective study was approved by the Institutional Review Board of ChangZheng hospital. Written informed consent was not obtained from each patient due to the study's retrospective design.

Data collection

The patients' clinical data, including history, laboratory findings and treatment, were obtained from medical records from the first encounter that eventually led to a diagnosis of DM-ILD. The clinical manifestations included cutaneous signs, muscle weakness and systemic complications. The patients also underwent biochemical assessments. Blood tests included evaluations for leukocytosis, platelet count, electrolytes, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), creatine kinase (CK), lactate dehydrogenase (LDH), aspartate transaminase (AST), alanine transaminase (ALT), rheumatoid factor (RF), and antinuclear antibody (ANA) and autoantibody screens.

ILD presentation

ILD was evaluated based on pulmonary high-resolution computed tomography (HRCT) scans of the lungs and respiratory symptoms. According to clinical presentation, patients were classified into two groups: acute/subacute or chronic ILD. Acute/subacute interstitial pneumonia was defined as rapidly progressive ILD within 3 months from the onset of symptoms. Chronic interstitial pneumonia was defined as asymptomatic non-rapidly progressive ILD or slowly progressive ILD over 3 months according to the International Consensus Statement of Idiopathic Pulmonary Fibrosis of the American Thoracic Society [12].

All 103 cases were categorized by their HRCT patterns. The categories included cryptogenic organizing pneumonia, nonspecific interstitial pneumonia and usual interstitial pneumonia. According to the Fleischner criteria [13], the HRCT images were assessed and categorized based on the following signs: consolidation, ground glass opacities, traction bronchiectasis, irregular linear opacities, bronchovascular bundle thickening, honeycombing and pleural effusion.

Statistical method

Quantitative data were described by the mean (median, range), and qualitative data were described as counts and percentages. The cumulative survival rate was calculated using the Kaplan-Meier method by Log rank test and the Cox proportional hazard model was used for univariate and multivariate analyses. Factors with a P value ≤ 0.10 were subjected to a multivariate analysis by Cox proportional hazards analysis. P values ≤ 0.05 were considered statistically significant. For group comparisons involving binary data, we used either the chi-square test (for sample sizes ≥ 5) or Fisher's exact test (for sample sizes ≤ 5). All statistical

Table 1. Patient characteristics and univariate analysis of the prognostic factors affecting overall survival in DM-ILD

Factors	DM with ILD (n=103)	Death (n=36)	Mortality by ILD (%)	*P* Value
General characteristics				
Age (<60/>60 y)	79/24	22/14	27.8 vs 58.3	0.003*
Sex (Female/Male)	76/27	29/7	38.2 vs 25.9	0.3
Clinical manifestations				
Fever (no/yes)	43/60	13/23	30.2 vs 38.3	0.487
Cough (no/yes)	37/64	13/23	35.1 vs 35.9	0.948
Dyspnea (no/yes)	60/43	17/19	28.3 vs 44.2	0.047*
Myalgia (no/yes)	82/21	29/7	35.4 vs 33.3	0.848
Esophageal involvement (no/yes)	84/19	26/10	31.0 vs 52.6	0.102
Limb muscle involvement (no/yes)	42/61	15/21	35.7 vs 34.4	0.899
Neck muscles (no/yes)	89/14	31/5	34.8 vs 35.7	0.686
Scapular muscles involvement (no/yes)	67/36	24/12	35.8 vs 33.3	0.851
Pelvic muscles involvement (no/yes)	56/47	21/15	37.5 vs 31.9	0.52
Raynaud's phenomenon (no/yes)	94/9	32/4	34.0 vs 44.4	0.424
Gottron's sign (no/yes)	40/63	10/26	25.0 vs 41.3	0.122
Heliotrope sign (no/yes)	49/54	12/24	24.5 vs 44.4	0.019*
Skin erythema (no/yes)	23/80	4/32	17.4 vs 40.0	0.061
Periungual erythema (no/yes)	96/7	32/4	33.3 vs 57.1	0.093
Arthralgia (no/yes)	56/47	20/16	35.7 vs 34.0	0.794
Morning stiffness (no/yes)	93/10	33/3	35.5 vs 30.0	0.412
Fatigue (no/yes)	33/70	10/26	30.3 vs 37.1	0.604
Form of ILD (chronic/acute, subacute)	55/48	13/23	52.1 vs 76.4	<0.0001*
Time of onset of ILD (Concomitant with/after/before DM)	73/18/13	25/9/2	34.2 vs 50.0 vs 15.4	0.262

ILD, interstitial lung disease. **p* value less than 0.05.

calculations were performed using SPSS version 19.0.

Results

Patient characteristics

Overall, 103 DM patients with ILD were enrolled in our study, including 77 females and 26 males, with a mean age of 51.2 years (range, 19-78 y). The mean follow-up period was 21.9 months (range, 2 w-120 month). Thirty-seven patents died during the follow-up period.

Clinical features and laboratory findings

Cutaneous signs (75.7%) and proximal muscle weakness (82.5%) were the most common manifestations at onset. Other manifestations included fatigue (67.9%), fever (58.2%), cough (62.1%), arthritis/arthralgia (45.6%), dyspnea (41.7%), myalgia (20.3%), dysphagia (18.4%), and Raynaud's phenomenon (8.7%).

Among the cutaneous manifestations, skin erythema (Shawl's sign and V-sign) (77.6%) was the most common, followed by Gottron's sign (61.1%) and heliotrope sign (52.4%). Other cutaneous manifestations, including mechanic's hand and periungual erythema, were found in only a few individuals. An individual patient could have multiple cutaneous signs simultaneously.

ILD onset preceded initial DM manifestations in 19 patients (18.4%) and occurred after DM onset in 12 patients (11.7%), and 72 patients (69.9%) were diagnosed concurrently with DM. According to lung manifestations, 48 patients (46.6%) were diagnosed with the acute/subacute form of ILD, and 55 patients (53.4%) were diagnosed with the chronic form of ILD. Based on pulmonary HRCT scan patterns, patients with ILD were classified into three groups. Nonspecific interstitial pneumonia was the most common type (n=62, 60.2%) of ILD,

Table 2. Lab findings and univariate analysis of the prognostic factors affecting overall survival in DM-ILD

Factors	DM with ILD (n=103)	Death (n=36)	Mortality by ILD (%)	*P* Value
Leukocyte (N/>10/<4×10^9/L)	65/23/14	22/9/4	33.8 vs 39.1 vs 28.6	0.661
Platelet (N/>300/<100×10^9/L)	73/20/8	25/5/5	34.2 vs 25.0 vs 62.5	0.118
Erythrocyte sedimentation rate (N/>20 mm/h)	36/64	8/28	22.2 vs 43.8	0.043*
Creactive protein (N/>10 mg/L)	53/50	12/24	22.6 vs 48.0	0.01*
Creatine kinase (N/>194 IU/L)	52/51	16/20	30.8 vs 39.2	0.462
Creatine kinase-MB (N/>25 IU/L)	59/42	20/14	33.9 vs 33.3	0.73
Aspartate amino transferase (N/>40 U/L)	53/46	17/18	32.1 vs 39.1	0.502
Alanine aminotransferase (N/>50 U/L)	60/43	18/18	30.0 vs 41.9	0.325
Alkaline phosphatase (N/>135 U/L)	86/10	29/5	33.7 vs 50.0	0.678
Lactate dehydrogenase (N/>215 U/L)	15/88	2/34	13.3 vs 38.6	0.051
Serum calcium (N/<2.25 mmol/L)	36/56	4/28	11.1 vs 50.0	<0.0001*
Serum potassium (N/<135 mmol/L)	66/23	23/8	34.8 vs 34.8	0.747
Immunoglobulin G (N/>16.6 g/L)	60/42	18/18	30.0 vs 42.9	0.292
Complement 3 (N/>1.2 g/L/<0.8 g/L)	62/33/4	24/8/2	38.7 vs 21.9 vs 60.0	0.221
Complement 4 (N/>0.38 g/L/<0.16 g/L)	61/13/24	21/4/8	34.4 vs 30.8 vs 33.3	0.941
Antinuclear antibody (negative/positive)	64/26	26/7	40.6 vs 26.9	0.222
Anti-Jo1 (negative/positive)	82/7	31/1	37.8 vs 14.2	0.269
Anti-SSA (negative/positive)	73/12	28/4	38.4 vs 33.3	0.711
Anti-SMA (negative/positive)	86/3	31/1	36.0 vs 33.3	0.75

ILD, interstitial lung disease. *p value less than 0.05.

followed by usual interstitial pneumonia (n=25, 24.3%) and cryptogenic organizing pneumonia (n=16, 15.5%) (**Table 1**).

Laboratory tests showed that anti-nuclear antibody was positive in 26 patients, anti-SSA antibody was positive in 12 patients, anti-Jo-1 antibody was positive in 7 patients and anti-SMA antibody was positive in 3 patients. Other lab test results are shown in **Table 2**.

Treatment and causes of death

Corticosteroids combined with immunosuppressive agents were administered to all patients. Ten patients received intravenous methylprednisolone pulse therapy (500 mg/day for three days). Oral prednisolone was administered to 43 patients at 60-80 mg/day, 20 patients at 40-60 mg/day, 18 patients at 20-40 mg/day and 12 patients at 0-20 mg/day. Immunosuppressive agents included cyclophosphamide in 80 patients, cyclosporine in 15 patients, azathioprine in 8 patients, methotrexate in 6 patients, and hydroxychloroquine in 3 patients. In addition, 15 patients received intravenous immune globulin (IVIG).

Thirty-six DM patents with ILD died during the follow-up period. Of these, the causes of death included respiratory failure due to ILD progression (n=20), bacterial pneumonia (n=26), fungal pneumonia (n=14) and heart failure (n=3) (**Table 3**).

Univariate and multivariate analyses of factors associated with poor prognosis

In our series, the general characteristics, clinical symptoms and laboratory results of the patients were included in the statistical analysis using the Kaplan-Meier method. Factors that significantly shortened the mean survival time of ILD patients included acute/subacute form of ILD (P<0.0001, chi-square value: 14.361), age over 60 years (P=0.003, chi-square value: 9.113), heliotrope sign (P=0.019, chi-square value: 5.557), dyspnea (P=0.047, chi-square value: 3.934), ESR>20 mm/h (P=0.043, chi-square value: 4.098), CRP>10 mg/L (P=0.01, chi-square value: 6.557), and hypocalcemia (P<0.0001, chi-square value: 13.210). However, gender, arthralgia, the presence of ANA, anti Jo-1 or SSA antibody positivity, and CK or AST levels did not affect the survival of

Table 3. Treatment and outcome of DM-ILD

Treatment	DM with ILD (%)
Corticosteroids + Immunosuppressive agents	103 (100%)
Intravenous Methylprednisolone 500 mg x 3 day	10 (9.71%)
Oral Prednisolone 60-80 mg/d	43 (41.75%)
Oral Prednisolone 40-60 mg/d	20 (19.42%)
Oral Prednisolone 20-40 mg/d	18 (17.48%)
Oral Prednisolone 0-20 mg/d	12 (11.65%)
Cyclophosphamide	80 (77.67%)
Cyclosporin	15 (14.56%)
Azathioprine	8 (7.77%)
Methotrexate	6 (5.83%)
Hydroxychloroquine	3 (2.91%)
Intravenous Immuneglobulin	15 (14.56%)
Cause of death	36
Progression of ILD	20 (55.56%)
Bacterial Pneumonia	26 (72.22%)
Fungal Pneumonia	14 (38.89%)
Heart Failure	3 (8.33%)

Table 4. Multivariate analysis of the prognostic factors affecting overall survival in DM-ILD

Variables	B	HR (95% CI)	*P* Value
Age>60 y	0.838	2.311 (1.055-5.063)	0.036*
Heliotrope sign	0.931	2.538 (1.125-5.725)	0.025*
Acute/subacute form of ILD	1.643	5.173 (1.938-13.491)	<0.001*
Dyspnea	0.338	1.402 (0.634-3.098)	0.404
ESR>20	1.17	3.223 (1.170-8.882)	0.024*
CRP>10	1.007	2.738 (1.177-6.373)	0.019*
Hypocalcemia	1.118	3.058 (1.001-9.340)	0.05*
Periungual erythema	0.249	1.283 (0.401-4.106)	0.674
LDH>215	0.939	2.558 (0.477-13.730)	0.273

B, coefficient value; CI, confidence interval; HR, hazard ratio; y, years. *P value ≤ 0.05 for multivariate analysis.

ILD patients. The above factors, together with periungual erythema (P=0.093, chi-square value: 2.829), LDH>215 (P=0.051, chi-square value: 3.794), and skin erythema (P=0.061, chi-square value: 3.498), were confirmed in the multivariable analysis. The acute/subacute form of ILD (P<0.001), age over 60 years (P=0.036), heliotrope sign (P=0.025), ESR>20 mm/h (P=0.024), CRP>10 mg/L (P=0.019) and hypocalcemia (P=0.05) remained highly significant as independent predicators of poor prognosis in DM patients with ILD. Details are listed in **Table 4**. The Kaplan-Meier curves of overall survival for age, form of ILD, heliotrope sign, ESR>20 mm/h, CRP>10 mg/L and hypocalcemia for all patients are shown in **Figure 2**.

Surprisingly, a negative correlation was found between the levels of CRP and blood calcium (P=0.005). Additionally, a negative correlation between the levels of ESR and blood calcium was detected (P= 0.01) (**Figure 3**).

Discussion

This retrospective study included 103 consecutive DM-ILD patients and attempted to evaluate their clinical features and prognostic factors. Our data demonstrated that age over 60 years, the acute/subacute form of ILD, heliotrope sign, dyspnea, ESR>20 mm/h, CRP>10 mg/L, hypocalcemia, periungual erythema, and LDH>215 U/L were significant predictors of survival in univariate Cox proportional hazards models. Age over 60 years, the acute/subacute form of ILD, heliotrope sign, ESR>20 mm/h, CRP>10 mg/L and hypocalcemia were revealed as independent predictors of poor prognosis in patients with ILD. To the best of our knowledge, this retrospective study included the largest cohort of DM-ILD patients and provided new insight into serum calcium in the pathology of DM.

Our data first demonstrated that acute/subacute ILD progression was a strong predictor of poor outcomes in DM patients, consistent with a previous study conducted on myositis-associated interstitial lung disease. In our cohort, DM patients with acute/subacute ILD progression have a much lower five-year survival rate than those with chronic ILD (52.1% vs 76.4%, respectively), showing a similar trend compared with data from a Japanese cohort [6]. Therefore, DM patients with acute/subacute ILD progression may require intensive treatment and care.

Heliotrope sign is a highly characteristic skin lesion of DM and has been identified as a pre-

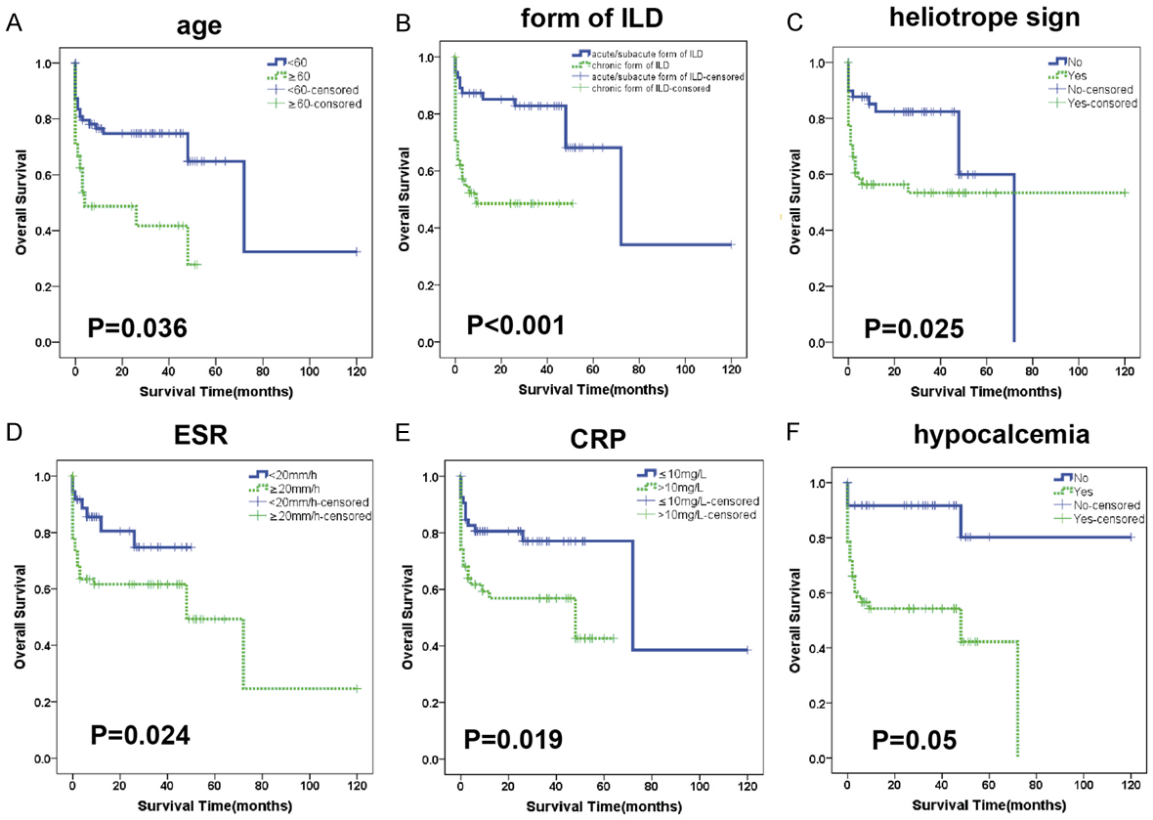

Figure 2. Kaplan-Meier curves of overall survival (A) age, (B) form of ILD, (C) heliotrope sign, (D) ESR, (E) CRP and (F) hypocalcemia.

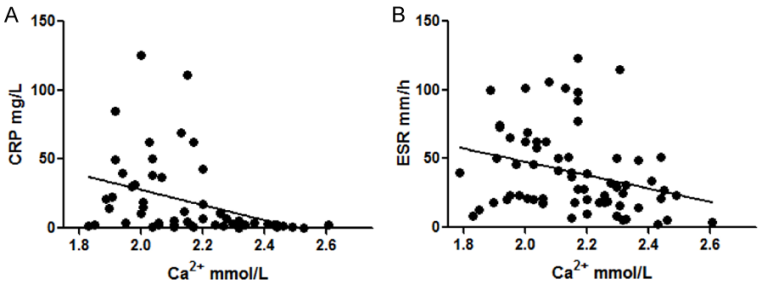

Figure 3. Correlations between level of serum calcium and (A) CRP (B) ESR.

dictor for the development of ILD. In our cohort, DM patients with heliotrope sign had a much higher mortality rate compared with those without heliotrope sign (44.4% VS 24.5%, respectively) in the follow-up. The current explanations for heliotrope sign include vacuolar alteration of the basal cell layer and mononuclear cell inflammatory infiltration [14, 15]. From this perspective, the emergence of heliotrope sign represents a state of severe vascular inflammation.

Our data also showed that high levels of ESR and CRP, which represent a state of high inflammation, were independent predictors of poor prognosis in patients with ILD. High cytokine profiles, including IL2, IL8, IL10 and TNF-α, were associated with disease activity, especially in DM-ILD [16-18]. These high levels of cytokines also indicated dramatic inflammation, which was consistent with high ESR or CRP levels. Decreased ESR or CRP levels could be associated with an improvement of ILD and a better prognosis. In addition, the levels of ESR or CRP may be potential biomarkers for treatment efficacy in ILD.

Remarkably, hypocalcemia was found to be an independent predictor of poor prognosis. Hypocalcemia is frequently observed in clinics, but it is often insufficiently addressed. Serum

calcium is essential for cellular functions, including muscle contraction and immune cell activation, and it maintains homeostasis with inorganic calcium [19]. Coincidently, calcinosis, which is the deposition of calcium in the skin and subcutaneous tissues, develops in nearly 20% of DM patients [20]. Calcinosis, with an underlying mechanism of vascular inflammation, is positively associated with longer disease duration and fingertip ulcers [20, 21]. Although calcinosis was not identified as an independent risk factor in our cohort because of unavailable data in the medical records, we assumed that it was one reasonable explanation for hypocalcemia in DM-ILD patients. Another explanation that we considered for hypocalcemia was excess serum calcium influx to immune cells, especially CD4+T cells in DM patients. CD4+T cells are implicated in the pathology of DM, including perifascicular atrophy, vasculopathy, and perivascular inflammation [22, 23]. Moreover, a markedly increased number of CD4+T cells was found in the bronchoalveolar lavage fluid of DM patients with ILD, indicating that pulmonary T cells play a role in the pathogenesis of DM-ILD [24]. Calcineurin inhibitors, including ciclosporin and tacrolimus, can inhibit calcium-induced T cell activation. Nagasaka *et al* retrospectively studied 32 patients with PM/DM-associated ILD who were treated with ciclosporin and corticosteroids; they found that ciclosporin had a crucial role in the early stage of induction therapy [25]. Some studies have also shown that the survival rate of DM-ILD improved with tacrolimus treatment [26, 27]. In addition, triple combination therapy with corticosteroids, calcineurin inhibitors and cyclophosphamide has been reported and has shown potential as an effective therapeutic strategy for rapid progressive interstitial lung disease [16]. Our findings provided evidence for the use of calcineurin inhibitors as induction and maintenance therapy for DM-associated ILD, especially for the acute/subacute form of ILD. Notably, our data showed a negative correlation between the level of serum calcium and ERS and CRP levels, suggesting that the level of serum calcium, especially hypocalcemia, may be an inflammatory biomarker for DM-ILD in clinics.

This study has some limitations. First, some patients who were seen at pulmonary or dermatology clinics were also enrolled in our retrospective study. Inevitably, some muscular or extra-muscular manifestations may not have been documented consistently, and arterial blood gases and pulmonary function were broadly analyzed. Therefore, these factors were not included in the univariate and multivariate analyses. Second, DM-specific or associated autoantibodies, such as anti-MDA5 [28], were not investigated in our study because these antibodies were not commercially available in our clinics. Third, the patients included in our study were from two different centers and were not treated with a standardized strategy. Most DM-ILD patients were treated with corticosteroids and immunosuppressive agents, but the immunosuppressive agents varied, and some patients were also treated with intravenous immunoglobulin, which may have affected the therapeutic outcomes.

In conclusion, the present cohort study demonstrated that the acute/subacute form of ILD, age over 60 years, heliotrope sign, ESR>20 mm/h, CRP>10 mg/L and hypocalcemia are independent predictors of poor outcomes in DM-ILD. Patients with these risk factors should be extensively evaluated and should receive intensive treatment. In addition, our data indicate the potential therapeutic effects of calcineurin inhibitors in DM-ILD. Furthermore, our data suggest that triple combination therapy should be considered in DM patients with rapid progressive interstitial lung disease.

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Disclosure of conflict of interest

None.

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