CLINICAL INVESTIGATION

Clinical and HRCT features of amyopathic dermatomyositis associated with interstitial lung disease: A retrospective study of 128 patients with connective tissue disease-related interstitial lung disease

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ABSTRACT

Background: This study retrospectively analyzed the laboratory data and chest images of patients with amyopathic dermatomyositis associated with interstitial lung disease (ADM-ILD) and patients with other connective tissue disease-related ILDs (CTD-ILDs) to find a characteristic index for the early recognition of ADM-ILD and help clinicians consider the possibility of ADM-ILD as soon as possible.

Methods: In our cohort study, the records of 128 Chinese patients with CTD-ILD, including 33 ADM-ILD patients, 37 rheumatoid arthritis (RA)-ILD patients, 33 primary Sjogren's syndrome (pSS)-ILD patients, 14 systemic sclerosis (SSc)-ILD patients and 11 systemic lupus erythematosus (SLE)-ILD patients. The patients' clinical features, laboratory parameters, and chest HRCT findings were analyzed.

Results: ADM-ILD patients generally had significantly higher LDH (333.52±160.21 U/L), AST (66.21±83.66 U/L), and CK-MB (18.23±8.28 U/L) levels than other CTD-ILD patients. A total of 90.91% (30/33) of ADM-ILD patients had elevated LDH. Patients with ADM-ILD were more prone to organizing pneumonia radiologic patterns on chest HRCT scans than patients with other CTD-ILDs (χ^2=37.39, $p < 0.001$) and were found in 18 of 33 ADM-ILD patients. Anti-MDA5 (45.45%) was the most commonly detected autoantibody in ADM-ILD patients, followed by anti-PL-7 (21.21%), anti-Jo-1 (12.12%), and anti-PL-12 (9.09%), and levels of ALT (96.93±119.79 vs. 17.50±6.218 U/L), AST (113.00±106.13 vs. 23.56±6.91 U/L), LDH (415.00±198.51 vs. 261.94±67.75 U/L) and CK-MB (22.57±5.91 vs. 14.61±8.36 U/L) were significantly higher in anti-MDA5-positive patients, but these patients had significantly lower WBC counts (4.82±2.61 vs. 7.14±3.00 × 10^9/L), lymphocyte counts (0.72±0.20 vs. 1.23±0.53 × 10^9/L), and ALB levels (31.90±4.76 vs. 35.49±4.71 g/L).

Conclusions: ADM-ILD patients have higher serum LDH, AST and CK-MB levels, especially serum LDH levels, and are more prone to organizing pneumonia radiologic patterns on chest HRCT scans than other CTD-ILD patients. A high level of serum LDH with ILD may be a useful characteristic index for recognizing ADM-ILD.

Keywords: Amyopathic dermatomyositis; Interstitial lung disease; Connective tissue disease-related interstitial lung disease; Lactate dehydrogenase. **[Am J Med Sci 2022;■(■):1–8.]**

INTRODUCTION

Idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of autoimmune diseases characterized by inflammation of the skeletal muscles. The most common subgroups in adults are dermatomyositis (DM), polymyositis (PM) and inclusion body myositis (IBM).[1] The clinical manifestations of IIM are diverse and are characterized by various degrees of muscle, skin, and lung involvement. Interstitial lung disease (ILD) is a common complication of IIMs that results in high mortality, with an estimated prevalence of 30%.[2–4] With the widespread awareness of myositis-specific autoantibodies (MSAs) and the myositis-associated autoantibody (MAA) spectrum, an increasing number of amyopathic dermatomyositis (ADM) cases have been diagnosed, especially with anti-melanoma differentiation-associated

gene 5 (MDA5) antibodies. ADM is defined as a subset of DM characterized by typical cutaneous manifestations of classic DM lasting 6 months or longer with no clinical evidence of muscular manifestations and no elevation in serum creatine kinase (CK).[5] There is a strong correlation between the incidence of ILD in IIM patients and myositis-specific autoantibodies. The incidence of ILD in MDA5-positive ADM patients is more than 90%,[6] and ADM-ILD with MDA5 positivity is characterized by a risk of rapidly progressive ILD (RP-ILD), which has an estimated prevalence of 26.8–62.5%, especially in East Asia,[7–13] and is often resistant to intensive therapy, such as high-dose corticosteroids combined with cyclosporine A (CsA), tacrolimus, or cyclophosphamide agents. The result is acute fatal respiratory failure, and the 6-month mortality rate is as high as 45.0–64.3%.[9,12,14]

Previous studies showed that patients who were treated intensively with combination immunosuppressive therapy upon diagnosis with ADM-ILD had better survival outcomes than those who received immunosuppressive therapy using a sequential approach after failure of the initial treatment.[15,16] Therefore, early diagnoses and timely treatment are very important for reducing the mortality of ADM-ILD.

However, ADM diagnosis has embraced the use of overlapping syndromes to account for clinical heterogeneity and the lack of muscular manifestations and elevated CK, making the diagnosis even more difficult. This study retrospectively analyzed the laboratory data and chest images of 128 patients with CTD-ILD, including 33 ADM-ILD patients, to establish a characteristic index for the early recognition of ADM-ILD and alert clinicians to the possibility of ADM-ILD as early as possible.

METHODS

Ethics approval and consent to participate

Written informed consent was obtained from all participants. The cohort study was approved by the institutional review board of the affiliated hospital of medical school of Ningbo university, Ningbo, China. (IRB no: KY20210905). Written informed consent from study subjects was waived because of the retrospective design.

Subjects

We retrospectively reviewed the medical records of patients who were diagnosed with ILD, including idiopathic pulmonary fibrosis (IPF), idiopathic interstitial pneumonia (IIP), connective tissue disease (CTD)-associated ILD, interstitial pneumonia with autoimmune features (IPAF), fibrotic hypersensitivity pneumonitis (HP), and ILDs related to occupational exposures, between January 2017 and November 2021 at the Affiliated Hospital of Medical School of Ningbo University. 150 patients diagnosed with CTD-ILD were screened (Fig. 1). The CTDs included were amyopathic dermatomyositis (ADM), rheumatoid arthritis (RA), primary Sjogren's syndrome (pSS), systemic sclerosis (SSc) and systemic lupus erythematosus (SLE). PM/DM with elevated CK and/or muscular manifestations were not included. The diagnosis of a specific CTD was based on validated classification criteria. ADM was diagnosed according to the Sontheimer criteria.[5] The diagnosis of ILD was made by high-resolution computed tomography (HRCT) of the chest.

The exclusion criteria were as follows: (1) patients with malignancy at the beginning of diagnosis (n = 4); (2) patients who met ≥2 CTD classification criteria (n = 7); (3) patients with a history of taking drugs that can cause hallmark cutaneous manifestations of CTD (n = 2); and (4) patients treated with systemic glucocorticoid and/or immunosuppressive therapy before the diagnosis of CTD-ILD (n = 7). In addition, 18 cases of ADM-ILD were provided by Ningbo First Hospital from January 2018 to November 2021. Finally, 128 patients (including 33 ADM-ILD patients, 37 RA-ILD patients, 33 pSS-ILD patients, 14 SSc-ILD patients and 11 SLE-ILD patients) were included in this study (Fig. 1).

Data collection

Clinical data, including detailed patient histories, clinical manifestations, laboratory results and chest HRCT images, were obtained from the medical records at the time of CTD-ILD diagnosis.

Clinical manifestations included (1) symptoms related to CTD, such as arthralgia, fever, rash, and Raynaud's phenomenon, and (2) symptoms related to ILD, such as dry cough, shortness of breath, exertional dyspnea, clubbed fingers, and crackles.

Laboratory parameters, including the white blood cell count, C-reactive protein, erythrocyte sedimentation rate, albumin, alanine aminotransferase, aspartate aminotransferase, creatine kinase, lactate dehydrogenase, immunoglobulin, antinuclear antibodies, anti-Jo-1 antibodies, myositis-specific antibodies, myositis-associated antibodies, etc., were tested in these patients upon enrollment.

HRCT findings

HRCT examinations of the lung were performed in 1.0 or 1.5 mm-thick sections to evaluate radiographic abnormalities. Independent, separate, retrospective reviews of the chest HRCT images of each patient were performed by two radiologists. The ILD patterns were classified according to the criteria of the 2013 ATS/ERS classification of idiopathic interstitial pneumonias (IIPs)[17] as follows: definite or probable usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), lymphoid interstitial pneumonia (LIP), organizing pneumonia (OP), and mixed patterns. The diagnosis of ILD radiologic pattern relied on consensus opinion from two radiologists.

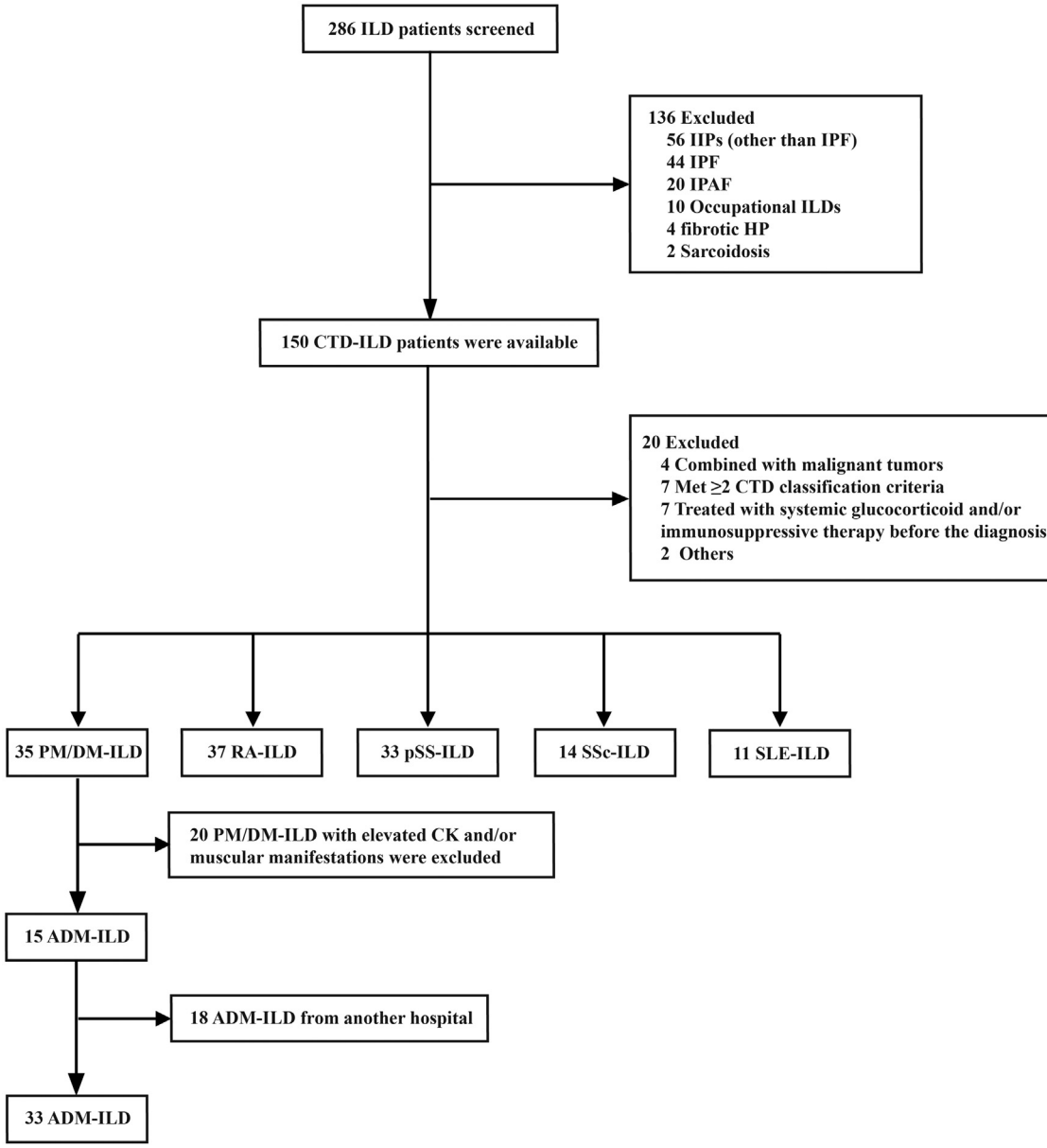

FIGURE 1. Flow chart of the study. ILD: interstitial lung disease; IIP: idiopathic interstitial pneumonia; IPF: idiopathic pulmonary fibrosis; IPAF: interstitial pneumonia with autoimmune features; HP: hypersensitivity pneumonitis; CTD: connective tissue disease; ADM: amyopathic dermatomyositis; RA: rheumatoid arthritis; pSS: primary Sjogren's syndrome; SSc: systemic sclerosis; SLE: systemic lupus erythematosus.

Statistical analysis

Continuous variables are expressed as the mean ± SD. The differences in clinical and laboratory data among CTD-ILD patients were analyzed by single-factor variance, and Dunnett's t test was adopted for multiple comparisons. For two-group comparisons of the binary data, either the chi-squared test or Fisher's exact test was used, t test was used in comparison of continuous data, and categorical data are expressed as positive "+" or negative "-". Statistical analyses were performed using GraphPad Prism 9 software and SPSS 24.0 statistical software. A p value < 0.05 was considered statistically significant.

RESULTS

Comparisons of clinical and laboratory data among ADM-ILD, RA-ILD, pSS-ILD, SSc-ILD and SLE-ILD patients

For all included patients, age, sex, clinical features, and laboratory data are summarized in Table 1. There were statistically significant differences in the white blood

TABLE 1. Comparison of clinical data and laboratory findings among ADM-ILD, RA-ILD, pSS-ILD, SSc-ILD and SLE-ILD.

	ADM-ILD	RA-ILD	pSS-ILD	SSc-ILD	SLE-ILD	*F* value	*p* value
Subjects (n)	33	37	33	14	11		
Age (years)	57.67±14.63	69.72±10.28	65.67±10.04	57.14±13.99	38.36±13.42		
M/F	9/24	16/21	4/29	3/11	2/9		
Fever	10 (30.30%)	8 (21.62%)	7 (21.2%)	2 (14.29%)	3 (27.27%)		
Cough	16 (48.48%)	19 (51.35%)	16 (48.48%)	5 (25.71%)	5 (45.45%)		
Dyspnea	18 (54.55%)	14 (37.84%)	11 (33.33%)	7 (50.00%)	2 (18.18%)		
Arthralgia	10 (30.30%)	30 (81.08%)	10 (30.30%)	4 (28.57%)	4 (26.36%)		
WBC (x109/L)	6.09±3.02	7.98±4.20	5.63±2.53	6.89±1.80	8.48±5.55	2.95	0.023
hsCRP (mg/L)	17.48±28.56	38.21±43.05	21.22±33.00	15.23±34.40	27.75±45.24	1.96	0.106
ESR (mm/h)	45.43±30.90	59.53±37.05	61.90±40.31	10.66±3.19	47.09±42.78	3.86	0.006
ALB (g/L)	33.86±5.00	34.88±4.68	37.03±4.76	39.87±3.85	37.69±3.35	5.55	<0.001
ALT (U/L)	53.62±88.95	19.92±18.23	22.00±14.61	25.79±24.16	20.45±14.39	2.71	0.033
AST (U/L)*	66.21±83.66	27.41±22.05	32.97±16.45	25.64±12.54	22.27±10.17	3.92	0.005
LDH (U/L)*	333.52±160.21	198.76±62.38	196.34±54.18	194.71±31.31	195.91±52.16	12.35	<0.001
CK (U/L)	77.47±33.08	56.14±34.99	51.84±29.20	89.79±69.57	79.18±106.14	2.60	0.040
CK-MB (U/L)*	18.23±8.28	11.11±4.54	10.66±3.19	12.79±4.69	10.55±6.28	9.76	<0.001
IgG (g/L)	15.36±3.53	14.46±4.14	19.38±6.52	14.22±2.13	23.26±10.90	8.03	<0.001

Data are presented as the mean (M)±standard deviation (SD), and $p < 0.05$ was considered significant.
ADM: amyopathic dermatomyositis; RA: rheumatoid arthritis; pSS: primary Sjogren's syndrome; SSc: systemic sclerosis; SLE: systemic lupus erythematosus; ILD: interstitial lung disease; M: male; F: female; WBC: white blood cell; hsCRP: high sensitivity C-reactive protein; ESR: erythrocyte sedimentation rate; ALB: albumin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; LDH: lactate dehydrogenase; CK: creatine kinase; CK-MB: creatine kinase and its MB isoenzyme; IgG: immunoglobulin G.
* The normal laboratory values of AST, LDH and CK-MB were (15−35) U/L, (106−211) U/L and (0−24) U/L, respectively.

cell (WBC), platelet, lymphocyte, erythrocyte sedimentation rate (ESR), albumin (ALB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), creatine kinase (CK), creatine kinase-MB (CK-MB) and IgG. Furthermore, through multiple comparisons between ADM-ILD and other types of CTD-ILD, we found that ADM-ILD patients generally had higher AST, LDH and CK-MB levels than other CTD-ILD patients, and the difference was statistically significant (Fig. 2); 42.42% (14/33), 90.91% (30/33) and 27.27% (9/33) of ADM-ILD patients had elevated AST, LDH and CK-MB levels, respectively. We also evaluated multiple comparisons between patients with other types of CTD-ILDs and ADM-ILD patients with or without anti-MDA5 positivity. ADM-ILD patients with or without anti-MDA5 positivity had significantly higher LDH levels than other CTD-ILD patients (Supplement 1). However, there were no significant differences in their levels of AST and CK-MB.

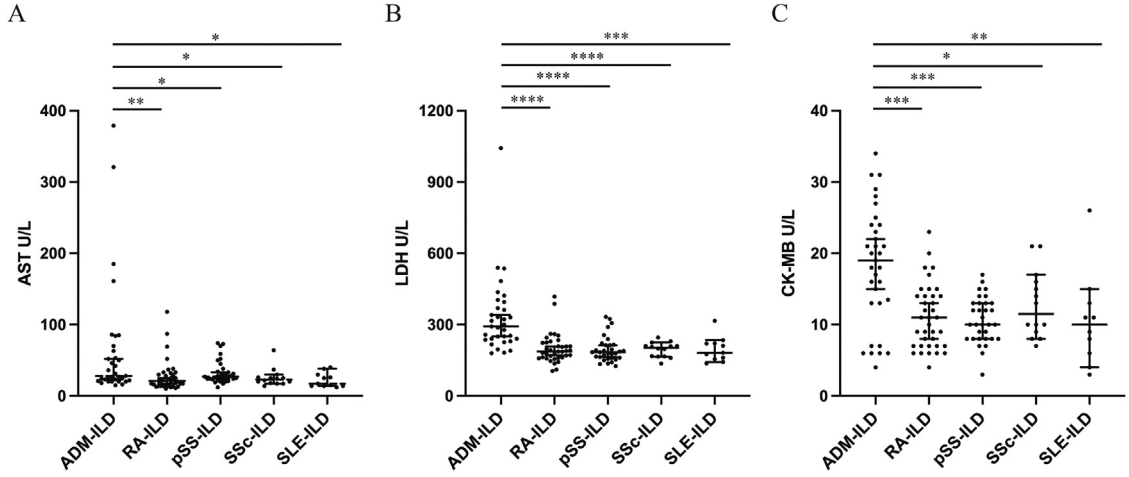

FIGURE 2. ADM-ILD patients had significantly higher AST (A), LDH (B), and CK-MB (C) levels than other CTD-ILD patients. Abbreviations described in Figure 1. *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$; ****: $p < 0.0001$.

TABLE 2. ILD radiologic patterns among ADM-ILD, RA-ILD, pSS-ILD, SSc-ILD and SLE-ILD.

	ADM-ILD	RA-ILD	pSS-ILD	SSc-ILD	SLE-ILD
UIP	0% (0/33)	43.24% (16/37)	9.09% (3/33)	14.29% (2/14)	18.18% (2/11)
NSIP	39.39% (13/33)	37.84% (14/37)	60.61% (20/33)	85.71% (12/14)	72.73% (8/11)
OP	54.55% (18/33)	13.51% (5/37)	0% (0/33)	0% (0/14)	9.09% (1/11)
LIP	0% (0/31)	0% (0/37)	24.24% (8/33)	0% (0/14)	0% (0/11)
Unclassified	6.06% (2/33)	5.41% (2/37)	6.06% (2/33)	0% (0/14)	0% (0/11)

ADM: amyopathic dermatomyositis; RA: rheumatoid arthritis; pSS: primary Sjogren's syndrome; SSc: systemic sclerosis; SLE: systemic lupus erythematosus; ILD: interstitial lung disease; UIP: usual interstitial pneumonia; NSIP: nonspecific interstitial pneumonia; LIP: lymphoid interstitial pneumonia; OP: organizing pneumonia.

HRCT findings

The ILD radiological patterns of patients with ADM-ILD and other CTD-ILD are shown in Table 2. We divided them into the ADM-ILD group (n = 33) and the other CTD-ILD group (n = 95). Patients with ADM-ILD were more prone to OP radiologic patterns on chest HRCT scans than patients with other CTD-ILDs, and the difference was statistically significant (χ^2=37.39, $p < 0.001$). However, there was no difference between the ADM-ILD and other CTD-ILD groups in NSIP radiologic patterns (χ^2=2.99, p = 0.084).

Clinical characteristics of ADM-ILD patients

Demographic, skin manifestation, laboratory parameter, antinuclear antibody and ILD radiologic pattern data are shown in Table 3. The mean age at ADM-ILD diagnosis was 57.67 ± 14.63 years, and the ratio of

TABLE 3. Clinical data, laboratory data, and ILD radiologic patterns in all patients, anti-MDA5-positive patients, and anti-MDA5-negative patients.

	All patients (n = 33)	anti-MDA5 + (n = 15)	anti-MDA5 – (n = 18)	p value
Age (years)	57.67±14.63	49.80±14.37	64.22±11.53	0.026
M/F	9/24	2/13	7/11	0.134
Fever	10 (30.30%)	7 (46.67%)	3 (16.67%)	0.126
Cough	16 (48.48%)	7 (46.67%)	9 (50.00%)	>0.999
Dyspnea	18 (54.55%)	8 (53.33%)	10 (55.56%)	>0.999
Arthralgia	10 (30.30%)	5 (33.33%)	5 (27.78%)	>0.999
Rash				
Gottron's sign	19 (57.58%)	11 (73.33%)	8 (44.44%)	0.158
Heliotrope rash	16 (48.48%)	10 (66.67%)	6 (33.33%)	0.084
WBC (x109/L) *	6.09±3.02	4.82±2.61	7.14±3.00	0.026
Lym (x109/L) *	1.00±0.49	0.72±0.20	1.23±0.53	0.001
hsCRP (mg/L)	17.48±28.56	9.31±10.46	24.29±36.57	0.136
ESR (mm/h)	45.43±30.90	48.38±22.46	43.18±36.60	0.655
ALB (g/L) *	33.86±5.00	31.90±4.76	35.49±4.71	0.038
ALT (U/L) *	53.62±88.95	96.93±119.79	17.50±6.21	0.008
AST (U/L) *	66.21±83.66	113.00±106.13	23.56±6.91	0.001
LDH (U/L) *	333.52±160.21	415.00±198.51	261.94±67.75	0.004
CK (U/L)	77.47±33.08	82.79±25.74	73.33±38.04	0.432
CK-MB (U/L) *	18.23±8.28	22.57±5.91	14.61±8.36	0.004
IgG (g/L)	15.36±3.53	14.24±4.14	16.21±2.84	0.147
ANA >1:80 (n)	25 (75.76%)	11 (73.33%)	14 (77.78%)	>0.999
Oxygenation index	330.00±73.70	321.89±102.75	333.25±62.84	0.759
AaDO2	42.56±24.47	54.30±22.01	37.87±24.48	0.170
Radiologic pattern				
OP	18 (54.55%)	11 (73.33%)	7 (38.89%)	0.080
NSIP	13 (39.39%)	2 (13.33%)	11 (61.1%)	0.011

Data are presented as the mean (M)±standard deviation (SD), and $p < 0.05$ was considered significant.
ADM: amyopathic dermatomyositis; ILD: interstitial lung disease; MDA5: melanoma differentiation-associated gene 5; M: male; F: female; WBC: white blood cell; Lym: lymphocyte; hsCRP: high sensitivity C-reactive protein; ESR: erythrocyte sedimentation rate; ALB: albumin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; LDH: lactate dehydrogenase; CK: creatine kinase; CK-MB: creatine kinase and its MB isoenzyme; IgG: immunoglobulin G; ANA: antinuclear antibody; $AaDO_2$: alveolar-arterial oxygen difference; OP: organizing pneumonia; NSIP: nonspecific interstitial pneumonia.
* The normal laboratory values of WBC, Lym, ALB, ALT, AST, LDH and CK-MB were (3.5–9.5) × 10^9/L, (1.1–3.2) × 10^9/L, (40–55) g/L, (9–50) U/L,(15–35) U/L, (106–211) U/L and (0–24) U/L, respectively.

TABLE 4. The detection of myositis autoantibodies in ADM-ILD patients.

	All patients (n = 33)
MSAs	
Anti-MDA5	15 (45.45%)
Anti-Jo-1	4 (12.12%)
Anti-PL-7	7 (21.21%)
Anti-PL-12	3 (9.09%)
Anti-EJ	3 (9.09%)
Anti-OJ	1 (3.03%)
Anti-SRP	1(3.03%)
MAAs	
Anti-Ro-52	17 (51.52%)
Anti-PM-Scl 100	1 (3.03%)
Anti-PM-Scl 75	1 (3.03%)

ADM: amyopathic dermatomyositis; ILD: interstitial lung disease; MSA: myositis-specific autoantibody; MAA: myositis-associated autoantibody; MDA5: melanoma differentiation-associated gene 5; Jo-1: histidyl-tRNA synthetase; PL-7: threonyl-tRNA synthetase; PL-12: alanyl-tRNA synthetase; EJ: glycyl-transfer ribonucleic acid synthetase; OJ: isoleucyl-tRNA synthetase; SRP: signal recognition particle; PM-Scl: polymyositis/Scl.

females to males was 2.67:1. Common clinical manifestations included dyspnea (54.55%), cough (48.48%), fever (30.30%) and arthralgia (30.30%). Gottron's sign (57.58%) and heliotrope rash (48.48%) were common in those patients, especially in anti-MDA5-positive patients. High levels of ESR, LDH, ALT, AST, and immunoglobulin G (IgG) were common in ADM-ILD patients, while the levels of serum albumin (ALB) and lymphocyte count were lower than normal values. CK, CK-MB and high sensitivity C-reactive protein (hsCRP) were always in the normal reference range. The detection of myositis autoantibodies in ADM-ILD patients are shown in Table 4. In the detection of MSAs in our study, anti-MDA5 was the most commonly detected autoantibody (45.45%). Anti-aminoacyl-tRNA synthetase antibodies (anti-ARS) were relatively less common in ADM-ILD. The positive rate of anti-PL-7 was 21.21%, followed by anti-Jo-1 (12.12%), anti-PL-12 (9.09%), anti-EJ (9.09%) and anti-OJ (3.03%). Anti-Ro-52 had the highest positivity rate (52.4%) among the MAAs. Other MAAs, such as anti-PM-Scl100 (3.03%) and anti-PM-Scl75 (3.03%), were less frequent in ADM-ILD.

When compared to ADM-ILD with anti-MDA5-positive patients and anti-MDA5-negative patients, anti-MDA5-positive patients tended to have a younger onset age (with a mean age of 49.80±14.37 years); levels of ALT (96.93±119.79 vs. 17.50±6.218 U/L), AST (113.00±106.13 vs. 23.56±6.91 U/L), LDH (415.00±198.51 vs. 261.94±67.75 U/L) and CK-MB (22.57±5.91 vs. 14.61±8.36 U/L) were significantly higher in anti-MDA5-positive patients; and levels of WBC (4.82±2.61 vs. 7.14±3.00 × 10^9/L), lymphocyte count (0.72±0.20 vs. 1.23±0.53 × 10^9/L), platelet count (200.40±66.83 vs. 239.56±38.47 × 10^9/L), and ALB (31.90±4.76 vs. 35.49±4.71 g/L) were significantly lower in anti-MDA5-positive patients.

DISCUSSION

In the present study, we retrospectively reviewed 128 cases of CTD-ILD, including 33 ADM-ILD patients, and assessed their clinical features. Our findings demonstrated that ADM-ILD patients generally had higher AST, LDH and CK-MB levels than other CTD-ILD patients, and 90.91% of ADM-ILD patients had elevated LDH. OP is the most common ILD radiologic pattern, and anti-MDA5 was the most commonly detected autoantibody in ADM-ILD patients, followed by anti-PL-7, anti-Jo-1, anti-PL-12 and anti-EJ. In addition, we divided ADM-ILD into two groups and demonstrated that ADM-ILD with anti-MDA5-positive patients had higher levels of ALT, AST, LDH and CK-MB but had lower levels of WBC, lymphocyte count and ALB.

ADM-ILD patients with MDA5 positivity had higher risk for RP-ILD than those with other myositis-specific antibody positivity,[11–13] and ADM-ILD with MDA5 positivity is often resistant to intensive therapy. The 6-month mortality rate is as high as 45–64.3%.[9,12,14] Go et al.[15] analyzed 47 Japanese patients with DM-ILD, including 19 ADM-ILD patients. They found that early CsA treatment was associated with better survival in patients with ADM-ILD, and the 5-year survival rate was as high as 75%. Recent studies have shown that tofacitinib may be beneficial to patients with ADM-ILD who are anti-MDA5 positive,[18–20] and the 6-month survival rate is as high as 60–100%. Therefore, early diagnoses and timely treatment are very important to reduce the mortality of ADM-ILD.

ADM with anti-MDA5 antibodies had the characteristic skin rash of the disease, Gottron's sign and heliotrope rash[21–23]; however, Gottron's sign and heliotrope rash did not appear in all ADM patients. Our present study showed that 57.58% and 48.48% of AMD-ILD patients developed Gottron's sign and heliotrope rash, respectively. In addition, most ADM-ILD patients first visit the respiratory department because of shortness of breath, cough, fever and other symptoms, and non-rheumatologists may not notice these characteristic rashes. Consequently, patients may be diagnosed with only IIPs or interstitial pneumonia with autoimmune features (IPAF), resulting in missed opportunities for active treatment and close monitoring and disease progression over time. In our study, we found that ADM-ILD patients had higher LDH levels than other CTD-ILD patients; in 90.91% of ADM-ILD patients, the LDH level exceeded the normal reference value, while this value was exceeded in only 28.42% of other CTD-ILD patients. Furthermore, subgroup analysis showed that ADM-ILD patients with or without anti-MDA5 positivity had higher LDH levels than other CTD-ILD patients. Previous studies have also shown that LDH is elevated in ADM-ILD and is related to a poor prognosis.[9,14,24,25] This suggests that ILD patients

with an LDH increase above the normal reference value should be alert to the possibility of ADM-ILD. Therefore, for patients with suspected CTD-ILD and with elevated LDH, MSAs and MAAs need to be tested.

ILD is a common complication of ADM that results in high mortality.[22,24–29] Our study showed that ADM-ILD patients are more prone than patients with other CTD-ILD to OP radiologic patterns on chest CT scans. Previous studies have shown that ADM-ILD with anti-MDA5 antibodies is characterized by predominant subpleural and lower consolidation, random ground glass opacity (GGO) and the absence of intralobular reticular opacities and honeycomb,[25,30,31] suggesting a lower prevalence of a nonspecific interstitial pneumonia pattern and a higher prevalence of the OP pattern. Shao et al.[32] also found that the OP pattern was more common in patients with anti-MDA5 antibodies than in those without anti-MDA-5 antibodies, which is consistent with our research. Therefore, imaging findings of OP radiologic patterns are highly suggestive of ADM-ILD in CTD-ILD.

Previous studies have reported that ADM patients mostly have anti-MDA5-positive autoantibodies,[9,18,24,25,33] while only a few cases of ADM with other MSA antibodies have been reported.[21,34,35] Our study also showed that anti-MDA5 was the most commonly detected autoantibody, but anti-ARS was not rare. In addition, anti-MDA5-positive patients tend to have a younger onset age, and levels of ALT, AST and LDH were higher than those in anti-MDA5-negative patients, while WBC, lymphocyte count and ALB tend to decrease. Besides, the imaging features of anti-MDA5 ADM-ILD were similar to those of viral pneumonia which is sometimes difficult to distinguish from viral pneumonia, especially COVID-19 infection.[36–38] Interestingly, anti-MDA5 autoantibody was prevalent in COVID-19 patients and was correlated with severe disease and poor prognosis.[37] This supports that unidentified viral infection could induce MDA5 autoantibody and, subsequently, a maladaptive immune response resulting in disease.[39,40] Taken together, anti-MDA5 ADM-ILD needs to be considered when an ILD radiologic pattern of OP or NSIP with high levels of LDH, ALT and AST but low levels of WBCs and lymphocytes are observed.

There are several limitations to our study. First, it was a retrospective study, and the number of enrolled patients was small; therefore, it is possible that our findings do not represent the findings in larger patient populations. Second, limited clinical and laboratory data were available for review, and we did not analyze the correlation between the HRCT findings and histopathologic findings. Third, there was no comparison of forced vital capacity (FVC) and diffusion capacity for carbon monoxide (DLCO) between ADM-ILD and other CTD-ILD, mainly because data for these key parameters of pulmonary function were missing for many of our patients. Fourth, some negative or positive associations in the statistical analyses may have been due to inadequate power due to the small sample size. Therefore, a prospective study with a substantially larger sample size and a randomized controlled trial are needed to further validate our findings.

CONCLUSIONS

In conclusion, our study found that ADM-ILD patients have higher serum LDH, AST and CK-MB levels and are more prone to OP radiologic patterns on chest HRCT scans than other CTD-ILD patients. A high level of serum LDH with ILD may be a useful characteristic index to prompt ADM-ILD. Therefore, ADM-ILD should be considered when patients with ILD have (1) Gottron's sign or heliotrope rash; (2) an ILD radiologic pattern of OP or NSIP or a mixture of the two; and (3) an unexplained increase in serum LDH above the relevant upper limit of normal.

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Supplement 1. ADM-ILD patients with or without anti-MDA5 positivity had significantly higher LDH levels than other CTD-ILD patients. *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$; ****: $p < 0.0001$.

DECLARATION OF COMPETING INTEREST

All authors have no conflicts of interest to disclose.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Tingting Wu: Conceptualization, Formal analysis, Data curation, Writing – original draft. **Haijun Zhou:** Data curation, Conceptualization, Formal analysis. **Suling Xu:** Data curation, Conceptualization, Formal analysis. **Zaichun Deng:** Conceptualization, Formal analysis. **Yun Zhang:** Data curation. **Qunli Ding:** Conceptualization, Formal analysis.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjms.2022.12.001.

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