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ORIGINAL ARTICLE

# Adult clinically amyopathic dermatomyositis with rapid progressive interstitial lung disease: a retrospective cohort study

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**Abstract** The aim of the study was to investigate the characteristics of adult clinically amyopathic dermatomyositis (CADM) with rapid progressive interstitial lung disease (ILD). Hospitalized patients with dermatomyositis (DM) and polymyositis (PM) between 1998 and 2005 in the Shanghai Renji Hospital were retrospectively studied. One hundred and forty-five patients were classified into CADM, classic DM or PM according to the modified Sontheimer's definition or Bohan–Peter's classification criteria. They were further stratified based on the presence or absence of clinical ILD. The Kaplan–Meier survival analysis and COX regression were performed. The predictive factors for ILD and other clinical properties of CADM-ILD were explored. The presence of clinical ILD was a significant risk factor for the poor outcome of DM/PM (OR=4.237, CI 95%: 1.239–14.49, $p$=0.021). Other risk factors are the presence of rashes and elevated urea nitrogen. Patients with DM/PM complicated by ILD had different clinical courses. Patients with CADM-ILD showed a rapidly progressive pattern with 6-month survival rate of 40.8%. The DM-ILD manifested a progressive pattern with a 5-year survival rate of 54%, while PM-ILD was chronic with 5- and 10-year survival rate of 72.4% and 60.3%, respectively. Better preserved muscle strength, elevated erythrocyte sedimentation rate, and hypoalbuminemia may herald ILD in DM/PM. Patients with CADM-ILD who later died had lower $PO_2$, higher lactate dehydrogenase, and prominent arthritis/arthralgia compared with those who survived. The presence of antinuclear antibody seems to be protective. Rapid progressive CADM-ILD is refractory to conventional treatment. ILD is a common complication in over 40% of our hospitalized DM/PM cohort and is also a prominent prognostic indicator. CADM is a special phenotype of DM/PM. CADM-ILD, which is usually rapidly progressive and fatal, requires further investigation.

**Keywords** Amyopathic · Dermatomyositis · Interstitial lung disease

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Interstitial lung disease (ILD) is a common complication of dermatomyositis (DM) and polymyositis (PM) with a prevalence of 5–65% [1]. Among these, a group of DM patients with characteristic cutaneous manifestations, negative anti-Jo-1 antibody and mild or even no myopathy, but prominent, rapidly progressive ILD have been encountered. In these patients, respiratory failure, and ultimately death is nearly inevitable, even after aggressive interventions. Such cases were reported in the past decade [2–7], mainly in the Asian regions, particularly in Japan. It is reasonable to postulate that this group of patients is a special phenotype of DM with racial propensity. Such patients are entangled with a disputable concept, amyopathic dermatomyositis (ADM or dermatomyositis sine myositis), which refer to patients with specific DM rashes persistent for more than 6 months to 2 years, but without substantial myositis. There are other patients who have typical DM skin lesions, but only subclinical or mild myopathy that were labeled as

hypomyopathic DM (HDM) [8]. Sontheimer [9] summarized these two conditions as clinically amyopathic DM (CADM). This retrospective hospitalized cohort study was conducted by adopting these definitions and classifications. The aim of this study was to delineate further the clinical course and risk factors of such CADM with rapid progressive ILD.

## Materials and methods

### Patients

Retrospectively, all DM/PM in-patients of the Shanghai Renji Hospital from January 1998 to August 2005 were gathered. All patients either fulfilled the Bohan–Peter DM/PM classification criteria [10] or followed the modified Sontheimer's definitions (1) ADM: with Gottron's rash or heliotrope rash, but with no symptoms or signs of muscle weakness, normal creatine kinase (CK), electromyography (EMG), and muscle biopsy. (2) HDM: with Gottron's rash or heliotrope rash, but with no symptom of weakness, normal or only mildly reduced muscle strength compatible to age, sex, and severity of systemic illness (should be higher than 4 in the 0–5 grade system). The CK was less than 1.5 times the upper normal limits. EMG was normal, or only with suspicious myopathic change, i.e., a slight increase of polyphasic potential. The pathological findings were normal or with scant lymphocyte infiltration with normal muscle structure. (3) The CADM is the combination of ADM and HDM. The EMG or biopsy was not available but fulfilled other definitions of ADM/HDM, was treated as possible CADM, and was also included. Duration of the disease is a variant under study, instead of a criterion. The clinical data including history and physical examination were documented. Rashes were graded as 0 (none), 1 (typical DM rashes), and 2 (typical DM rash superimposed with necrotic vasculitic components). Laboratory data, including muscle enzyme, antinuclear antibody (ANA, Hep2 cell substrate), anti-extractable nuclear antigen antibodies (ENAs, immune blotting test including anti-Jo-1 antibody), myositis specific antibodies (MSAs, Euroimmun kit, Germany), EMG, muscle pathology, chest radiography, pulmonary high resolution computed tomography (HRCT), management and complications were all documented. Outpatient follow-up was performed only for all surviving patients. Exclusive criteria included (1) overlap syndrome with other diffuse connective tissue diseases, secondary Sjogren syndrome was not excluded; (2) complicated with malignancy at any time; (3) juvenile DM/PM (disease onset at younger than 16 years of age); and (4) cases lost to follow-up (LTF). Those LTF patients were excluded in the survival analysis, but included in the cross-sectional study.

Thus, 242 hospitalized DM/PM patients were screened, out of which 19 (8.3%) had juvenile DM/PM, 17 (7.4%) suffered overlap syndrome, including overlap with systemic lupus erythematosus (SLE) in 10 (9 adults and 1 child), overlap of rheumatoid arthritis was observed in 6, and systemic sclerosis (SSc) was found in 3 patients. Two patients had overlapped SSc+SLE+PM. Five patients (2.2%) complicated with malignancies, including non-Hodgkin's lymphoma (one patient), colon cancer (one patient), breast cancer (one patient), ovarian cancer (one patient), and thyroid carcinoma (one patient), all of them were excluded consequently. The 202 adult idiopathic inflammatory myopathy were included in this study and were further categorized into 37 CADM, 82 classic DM, and 83 PM. There were 57 patients lost to follow-up at the end point of the study (see flow chart in Fig. 1). The median follow-up time from disease onset to end point for the remaining 145 adult idiopathic DM/PM was 27 months (1.5–273 months). According to the documented EMG and muscle biopsy of CADM or DM patients (CADM+ classic DM, $n=74$), the negative predictive value of muscle strength and CK was 86.7% (Table 1). This yield supports our clinically based classification of possible CADM patients that may well belong to CADM.

### Stratification

Patients were stratified, according to the presence or absence of ILD, into: (1) Clinical ILD where there is dry cough, dyspnea on exertion, Velcro rales in lung bases combined with substantial ILD findings in chest X-ray and/or HRCT (evaluated by radiology expertise). Infection and drug-induced interstitial changes were ruled out, but secondary infection was not excluded. (2) Subclinical ILD where there is no symptom and signs, but only radiological mild ILD abnormalities, e.g., slight or focal reticular changes, lobular septal thickness, subpleural line formation. (3) Without ILD. Rapid progressive ILD is defined when the duration of onset of pulmonary symptom to respiratory failure is within 3 months.

### Statistics

Kaplan–Meier survival curve, COX regression, logistic regression, univariant analysis, one-way ANOVA, and $\chi^2$ tests were performed using the SPSS10.0 software (SPSS, Chicago, IL, USA). $p<0.05$ is considered significant.

## Results

The clinical data of 145 DM/PM patients were summarized in Table 2. Anti-Jo-1 antibody was found to be exclusively

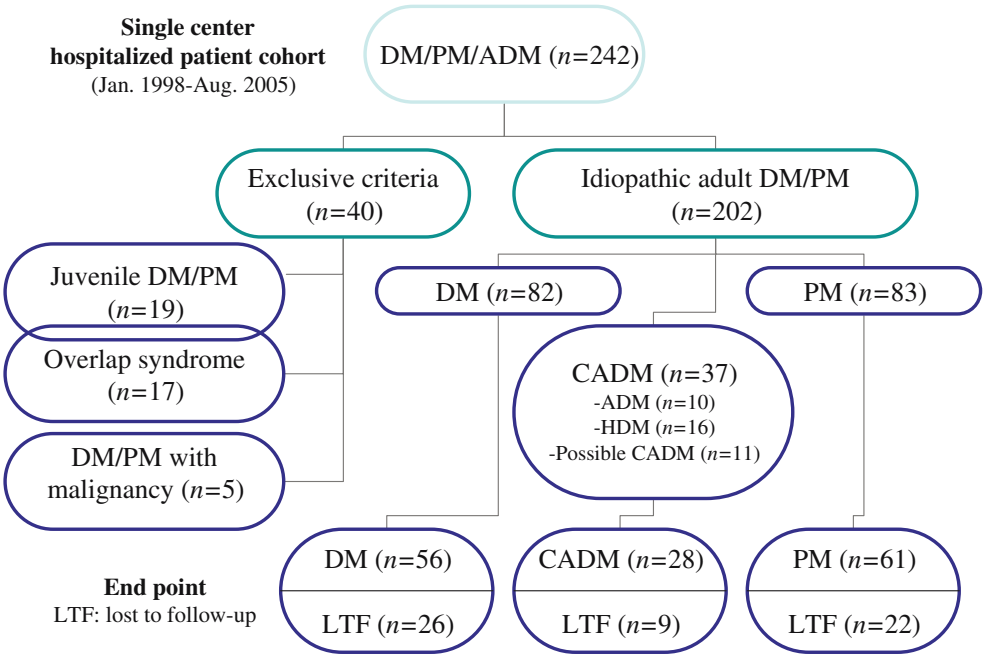


**Fig. 1** Flow chart of our single center hospitalized DM/PM patients' cohort

present in our PM patients. There was no significant correlation between tested MSAs and CADM.

## Survival analysis

Kaplan–Meier survival curve and COX regression show that (1) clinical ILD is the most prominent survival risk factor, odds ratio (OR)=4.237 (confident interval (CI) 95%: 1.239–14.49, $p$=0.021). On the other hand, the survival curve was not different between patients without ILD or subclinical ILD (Fig. 2a). The 5-year survival rates of DM/PM without ILD, with subclinical ILD or with clinical ILD were 87.5%, 89.2%, and 53.7%, respectively. Accordingly, the median survival times were 264, 144, and 79 months. (2) Presence of rashes (OR=2.905, CI 95%: 1.498–5.632, $p$=0.002) and elevated first available blood urea nitrogen (BUN, OR=1.067, CI 95%: 1.020–1.116, $p$=0.004) are other risk factors of DM/PM survival. Age, sex, fever, arthralgia or arthritis, muscle strength (including extremities, neck, pharyngeal, or bulb muscle involvement), first available muscle enzymes, serum albumin (ALB), globulin, creatinine, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ANA, and ENAs (including anti-Jo-1 antibody) are not identified as risk factors. (3) Clinical ILD complicated with CADM, classic DM or PM has different clinical courses (Fig. 2b). About 57% (12/21) of patients with CADM-ILD died because of progressive respiratory failure. Median time from onset of respiratory symptom to death is only 2 months (2 weeks to 7 months), which represented a rapid progressive pattern. From the disease onset, the 6 months survival rate of CADM-ILD was only 40.8%. The calculated median survival time was 10.2 months. On the other hand, DM-ILD showed a progressive pattern with a 5-year survival rate of 54% and median survival time of 90 months. The clinical course of PM-ILD was chronic. The 5- and 10-year survival rate was 72.4% and 60.3%, respectively, with median survival of 128 months.

## Predictive factors for clinical ILD in DM/PM

The overall prevalence of clinical ILD in our hospitalized idiopathic DM/PM cohort was 42.6% (86/202). For patients who were under follow-up, the prevalence was 48.3% (70/145). Logistic regression was performed on 202 DM/PM patients to find out extrapulmonary factors at disease onset, which could be of predictive value for clinical ILD. The result showed better-preserved proxi-

**Table 1** Predictive value of muscle strength and CK for muscle biopsy and EMG among our classic DM or CADM patients

| | Typical muscle biopsy or EMG finding | Normal or minor biopsy and EMG finding | |
|---|---|---|---|
| Decrease in muscle strength or CK>1.5 upper normal limits | 40 | 4 | PPV=90.9% |
| Normal muscle strength or CK<1.5 upper normal limits | 4 | 26 | NPV=86.7% |

**Table 2** Clinical features of 145 patients with adult idiopathic DM/PM

| | DM | | | | PM | |
|---|---|---|---|---|---|---|
| | CADM | | Classic DM | | | |
| | ILD+ | ILD− | ILD+ | ILD− | ILD+ | ILD− |
| No. of patients | 21 | 7 | 28 | 28 | 21 | 40 |
| Female (%) | 13(62) | 5(71) | 16(57) | 22(78) | 16(76) | 26(65) |
| No. of deceased | 12 | 0 | 12 | 5 | 6 | 1 |
| Age of onset of disease: year | 51±9 | 48±14 | 48±11 | 45±16 | 52±15 | 42±16 |
| Muscle strength 0–5 grade | 4.9±0.2 | 5±0 | 4.1±0.6 | 3.5±1.2 | 4.2±0.9 | 4.0±0.8 |
| Creatine kinase normal<190 u/L | 107±127 | 120±99 | 1420±2462 | 3364±6071 | 2938±2471 | 2792±2288 |
| ANA positive[b] /tested No. | 5/19 | 1/5 | 11/26 | 7/23 | 9/20 | 9/36 |
| +Jo-1(IBT)[c] | | | | | 5 | |
| MSAs tested No. | 10 | 7 | 9 | 19 | 7 | 10 |
| +Jo-1(ELISA)[c] | | | | | 5 | 2 |
| +Mi-2 | | 1 | | | | 2 |
| +ku 86 kDa | 2 | | 2 | 4 | | |
| +ku 72 kDa | | 2 | | 1 | | 1 |
| +PM-Scl | | | | 1 | 2 | |
| +PL-7 | | | 1 | 2 | | 1 |
| +PL-12 | | | | | | |

Numeric values are presented as mean±SD.
*MSAs*: myositis specific antibodies.
[a] ILD+/− refer to the presence or absence of clinical interstitial lung disease.
[b] ANA≥1:80 is considered as positive.
[c] Anti-Jo-1 antibody was detected by immune blotting test (IBT) and ELISA.

mal muscle strength (OR=3.222, CI 95%: 1.704–6.095, $p<0.001$) and elevation of first available ESR (OR=1.031, CI 95%: 1.008–1.054, $p=0.007$), which are positively correlated with ILD. First available ALB (OR=0.877, CI 95%: 0.793–0.972, $p=0.012$) has a negative correlation with ILD. These but not age, sex, fever, rash, arthralgia or arthritis, neck or bulb muscle involvement, first available enzyme profile, renal function, globulin level, CRP, rheumatoid factor, and ANAs (Jo-1, SSA, SSB, RNP), could be considered as ILD predictive factors.

## Clinical features of CADM

(1) Median time interval of cutaneous to myositis manifestation was 0.95 month (CI 95%: 11.2–12.2 months, $n=72$) in our classic DM patients with available data. In other words, the majority of classic DM patients in our cohort will have their rash and myositis within 1 year. There is no difference between those with and without clinical ILD (Fig. 3, left panel). (2) The follow-up time of CADM in this study was 1–63 months. Again, more than half of CADM-ILD patients died within 1 year (Fig. 3, right panel). While CADM patients who have disease duration longer than 24 months (8/28) have a favorable outcome, 2 of those 8 patients had cessation therapy with follow-up for 32 and 63 months. (3) Comparing patients with CADM-ILD with rapid progressive ILD who died ($n=12$) with those with CADM-ILD who survived ($n=9$) showed that the deceased had lower arterial blood $PO_2$ ($p=0.02$), higher LDH ($p=0.005$), negative or low titer of ANA ($p=0.044$), and

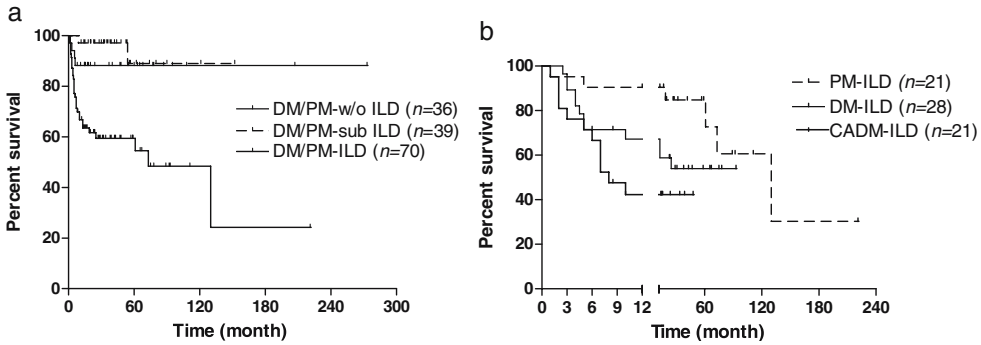


**Fig. 2** **a** Kaplan–Meier survival curve of DM/PM with clinical ILD (DM/PM-ILD) is different from that of DM/PM without ILD or with subclinical ILD, $p=0.0001$ and 0.013, respectively. **b** The survival curves of CADM-ILD and DM-ILD are different from that of PM-ILD with $p=0.004$ and 0.046, respectively

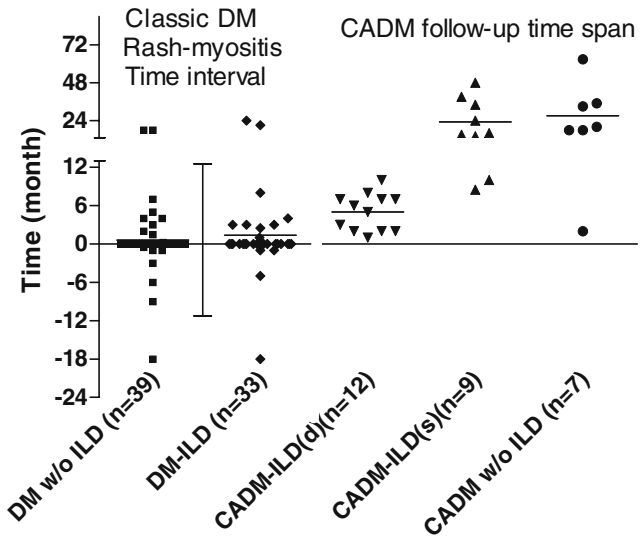


**Fig. 3** Comparison of the time interval between the onset of typical rash and myositis in classic DM patients (mean=0.95 month with CI 95%: –11.2–12.2 months, represented by the *error bar*, $n$=72) (*left panel*) and the time course of CADM-ILD those deceased (*d*) or surviving (*s*), and CADM without ILD (*right panel*)

prominent arthralgia or arthritis ($p$=0.018) (Table 3). There were no differences in age, sex, fever, first available CK, GOT, ALB, globulin, renal function test, rheumatoid factor, SSA/B, and RNP. Jo-1 antibody was absent in either of those patients. (4) Treatment of CADM: Patients without ILD received medium to low dose of corticosteroid (prednisone <0.5 to 1 mg/kg/day), while those with CADM-ILD received larger dosages (≥1 to 2 mg/kg/day) and some undertook methylprednisolone IV pulse therapy. Most of CADM-ILD patients were treated with a combination of cytotoxic agents, i.e., azathiaprine, cyclophosphamide, cyclosporine, mycophenolate mofetil (MMF), etc. Intravenous immunoglobulin was commonly introduced, in addition to other supportive care, but was unsuccessful to those deceased.

## DM/PM death review

There were 36 deaths in 145 adult idiopathic DM/PM under follow-up (24.8%). (1) The direct causes of deaths include ILD and its complications, i.e., respiratory failure, pneumomediastinum or pneumothorax, secondary infection that account for 69.4% (25/36) of death events. Infections not related to ILD account for another 25% (9/36), i.e., 1 suffered from aspiration pneumonia, 1 from disseminated tuberculosis, 1 from neutropenia due to azathiaprine, 1 patient having facial abscess with septicemia who had previous spleenectomy history, and miscellaneous infection in other 5 patients. One patient with HBV positive DM died to hepatic failure after immunosuppressive therapy; one died from congestive heart failure. (2) ILD was the direct cause of death in all deceased 12 CADM patients. The same reason accounts for 9 deaths in DM patients, whose median survival time was 5 months (2.5–25 months). Out of 9 patients, 5 died within the first 6 months of DM onset. Four PM patients died because of ILD, 1 of them only survived for 1 month, while the other 3 survived for 19–73 months. In summary, the onset of DM-ILD sometimes, and PM-ILD occasionally, may also have rapid progressive ILD patterns. (3) Pneumomediastinum or pneumothorax has an incidence of 8.6% (6/70) among DM/PM-ILD patients. Those 6 patients comprised 3 CADM-ILD, 2 DM-ILD, and 1 PM-ILD. Two out of 6 occurred after mechanical ventilation (noninvasive and invasive for each).

**Table 3** Clinical features of CADM patients with or without clinical ILD

| | CADM-ILD | | CADM without ILD |
|---|---|---|---|
| | Deceased | Survived | |
| No. of patients | 12 | 9 | 7 |
| $PO_2$ (mmHg) | 56±17* | 77±19 | – |
| LDH (normal<220 u/L) | 459±120** | 303±96 | 306±99 |
| ANA (≥1:80)/no. of patients tested | 1/11* | 4/8 | 1/5 |
| Arthritis or arthralgia | 8* | 1 | 2 |
| Treatment | | | |
| Glucocorticoid dosage (no. of patients) | >2 mg/kg/day (8)<br>1–2 mg/kg/day (4) | >2 mg/kg/day (1)<br>1–2 mg/kg/day (5)<br>1 mg/kg/day (3) | 1 mg/kg/day (3)<br>0.5–1 mg/kg/day (1)<br><0.5 mg/kg/day (3) |
| Cytotoxic agents (frequency in patients) | AZA (4), CTX (2), CsA (2), MMF (2), colchicines (4) | AZA (4), CTX (3), MMF (1), colchicines (1) | MTX (2), AZA (2), T2 (1), colchicines (1) |

*LDH*: lactate dehydrogenase; *AZA*: azathioprene, *CTX*: cyclophosphamide, *CsA*: cyclosporine A, *MMF*: mycophenolate acid, *MTX*: methotrexate, *T2*: *Tripterygium wilfordii*.

*$p$<0.05, **$p$<0.01 (compared between deceased and surviving CADM-ILD patients).

All 6 died without exception. This suggested that spontaneous pneumomediastinum or pneumothorax is a severe complication of DM/PM-ILD and may indicate poor prognosis [11, 12].

## Discussion

The goal of this study was to investigate a group of DM who have mild or even no myositis, but prominent rapid progressive fatal ILD. Some patients may even mimic severe acute respiratory syndrome (SARS), which had its pandemic episode in China in 2003. However, our patients were sporadic with no evidence of trans-infection and had ruled out SARS particularly during that pandemic period. There were similar cases reported worldwide [2–7], but mainly in Asia, which suggest that this may be a special phenotype of DM and probably has ethnic tendency. To our knowledge, this is the largest retrospective cohort study and may provide some useful information to delineate several important issues for this entity.

*ADM* It is still debatable whether ADM is an independent phenotype of DM. The indisputable fact is that 5–25% of DM patients present as cutaneous lesion only and a large proportion of them seem not to develop myositis even after a long-term follow-up [8]. There are also some patients manifesting HDM with only subclinical myopathy, which in turn relies on the sensitivity of laboratory techniques, e.g., EMG, muscle biopsy, imaging study (MRI). Technically, ADM and HDM cannot be clearly distinguished. Sontheimer who advocated ADM as a unique entity for 20 years, had proposed "clinically ADM" to encompass ADM and HDM [9]. In his comprehensive commentary, he quoted Confucius's words, "If names are not correct, language is not in accordance with the truth of things. If language is not in accordance with the truth of things, affairs cannot be carried out to success." Recently, more than 300 CADM cases presented in the literature had been summarized [13]. To facilitate our study, we further specified the classification of CADM. Sontheimer's CADM criteria include time limitations, those who have more than 6-months history are labeled with provisional CADM and longer than 24 months duration makes a definitive diagnosis. Our data showed that prognosis is favorable for the CADM patients with disease duration longer than 24 months. The results are consistent with dermatologic ADM literature [14]. On the other hand, more than half of our CADM-ILD died to rapid progressive ILD within 1 year. They could by no means fulfill Sontheimer's CADM definition. Such cases were referred to as "pre-myopathic DM" by others [13]. In our opinion, CADM-ILD is a significant phenotype in the spectrum of DM and should not be restricted by an artificial time frame. If the time frame is to be set up for CADM without ILD or chronic ILD, 12 months seem to be a better cutoff according to our results.

*ILD in DM/PM* ILD is a common complication of DM/PM. Survival analysis confirmed that clinical ILD is the most important risk factor for adult idiopathic DM/PM. On the contrary, subclinical ILD patients (at HRCT level) had no difference in chances of survival from those without ILD in our DM/PM cohort. Of note, HRCT is valuable in diagnosing ILD and an experienced clinician could identify usual interstitial pneumonia-like, nonspecific interstitial pneumonia (NSIP)-like, cryptogenic organizing pneumonia or bronchiolitis obliterans organizing pneumonia (BOOP)-like, diffuse alveolar damage (DAD)-like patterns [15] to postulate prognosis and determine management. On the other hand, appropriate evaluation of subtle ILD image abnormalities is prudent to avoid over therapeutic intervention. The COX regression indicated that DM rashes, in other words DM itself, is a poor prognostic factor among the DM/PM patients, especially when those rashes are superimposed with necrotic vasculitic component. Historically, such necrotic lesions had been related to malignancy [16], but were not the case in our idiopathic DM group. Twelve patients displayed those necrotic lesions (4 CADM and 8 DM) and 7 died (1 CADM and 6 DM). This sign may just indicate the severity of underlying disease, not necessarily favoring CADM or classic DM. Elevated BUN is an additional risk factor and the reason is still unclear. Disturbance of negative nitrogen balance in critically ill patients may be a possible explanation. Moreover, elevated BUN is a well-known indicator for severe pneumonia ("CURB" score) [17] regardless of any causes. Hence, BUN may relate to the severity of lung involvement in DM/PM patients. Our cross-sectional study suggested that when a DM/PM patient shows well-preserved muscle strength (amyopathic) and prominent inflammatory markers (ESR, ALB), physicians should be vigilant of subsequent ILD complication. Hypoalbuminemia may reflect both extent of (negative) inflammatory reaction and patients' poor general status, which deserves clinical concerns. Anti-Jo-1 antibody is a well-known MSA related to ILD. In our cohort, however, only 5 PM patients who had positive anti-Jo-1 and ILD were diagnosed as anti-Jo-1 syndrome. Those patients were characterized by chronic pulmonary fibrosis and underwent follow-up from 8.5 to 221 months, 2 of them died at 73 and 130 months, respectively. Our data did not show any correlation between anti-Jo-1 and ILD, which may be simply because of the low prevalence of this antibody in our cohort (less than 5% for IBT). The consistency of IBT and ELISA makes a laboratory error unlikely. Concerning other MSAs, there was no significant correlation between tested MSAs and

CADM. Of note, we have not observed a link between PL-7 and CADM in our patients, as a recent Japanese report claimed [18]. Open lung biopsy is the gold standard of ILD in DM/PM [19] with a better prognosis for patients with NSIP or BOOP and a devastating outcome for those with DAD. However, a pathologic type transformation was (from NSIP to DAD) reported [20, 21]. In this study, the open lung biopsy was done only in two patients, which was consistent with NSIP and BOOP, respectively. Another patient underwent autopsy, which revealed DAD and superimposed invasive *Aspergillus* infection.

*CADM presented as rapid progressive ILD* Our data showed that ILD complicated with CADM, classic DM or PM has distinct clinical courses. Reported prevalence of ILD in CADM varies from 0% to 83.3% [6, 15, 22]. This again may reflect referral and racial biases. In this study, 75% (21/28) of the CADM patients were complicated with ILD, among those 57% (12/21) died due to respiratory failure as a rapid progressive pattern. While DM-ILD shows a progressive pattern, the clinical course of PM-ILD is mainly chronic. These results are consistent with those of the Japanese [23] (which only compared DM-ILD and PM-ILD without CADM data) and the Korean [6] (small sample size with only six ADM) data. It is interesting to note that rapid progressive ILD is not unique in CADM, some DM-ILD and occasionally PM-ILD patients [24, 25] could also manifest as rapid progressive. Lower arterial $PO_2$, higher LDH, and prominent arthralgia or arthritis may be poor prognostic indicators for CADM-ILD. On the contrary, high titer positive ANA seems to be protective. Pulmonary function tests, FVC, and DLCO in particular, are important predictive factors for survival of clinical ILD [6]. However, in this retrospective study, those parameters were usually unavailable in severely ill patients referred to our center, and therefore, cannot be included in predictive evaluation. Established treatments for CADM-ILD do not exist yet and this poses a critical problem that needs a solution. Cyclosporine and/or cyclophosphomide are being recommended in the early phase of the disease by Japanese colleagues [25–27]. Swigris et al. showed that MMF could preserve pulmonary function in patients with connective tissue disease-related ILD in an open-label trial [28]. Five DM/PM patients were included but not specified. In our cohort, we also had a CADM-ILD case successfully treated with MMF, which was well-tolerated. There was anecdotal success by using autologous stem cell transplantation as well [29]. To our experience, over half of those patients may be refractory to all available interventions. With rapid deterioration, superimposed infection is almost inevitable, e.g., ventilator-related pneumonia, and hence, we do not recommend over-immunosuppression, including high dose IV pulse corticosteroids. However, appropriate immunosuppressive therapy and strong supportive care to help the patients transform from rapid progressive phase to chronic phase is a reasonable choice when a more effective intervention is still pending.

There are several intrinsic biases and limitations of this retrospective study: (1) High LTF rate in our cohort, which reached 28%. Shanghai is one of the largest cities in the world with 12 million registered residents along with 4 million unregistered populations. Patients not covered by medical insurance coming from all areas of China were also referred to our center to seek health care [30]. The existence of these patients probably may contribute to most of the LTF. In addition, in those, complicated with ILD in our cohort, the LTF rate was 18.6%. While in those without ILD, the rate was 35%. Thus, there may be overestimation of prevalence of ILD and death rate. (2) The subjects of this study were hospitalized patients in a referral hospital, a rheumatology center. From a dermatologist point of view, there will be underestimated prognosis for those CADM patients with cutaneous manifestation only. Hence, our results will greatly skew toward more severe conditions such as ILD. (3) There was a report suggesting a negative correlation between malignancy and ILD in DM/PM [31]. Indeed, malignancy in our cohort was quite low (only 2.2%), but the frequency of ILD was quite high, which again reflects the intrinsic bias of our cohort. (4) Lack of pulmonary function tests and open lung biopsy data were significant limitations of this retrospective study.

Despite these biases and limitations, this study could still support that CADM is likely to be a distinct subtype of idiopathic DM/PM and further confirmed that CADM-ILD is a special phenotype frequently presented as rapid progressive ILD. Sato et al. [32] had identified an anti-140 kDa unknown-protein antibody (anti-CADM-140) in some of their CADM patients related to ILD. Although still to be verified, it has provided important clue to finding biomarkers for CADM. Further investigation of the mechanism of CADM-ILD may help develop effective interventions. To facilitate exploring this clinical entity, in addition to Confucius' maxims, Shakespeare's words should also be borne in mind: "What's in a name? That which we call a rose, by any other name would smell as sweet".

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