Factors Associated with Interstitial Lung Disease in Patients with Polymyositis and Dermatomyositis: A Systematic Review and Meta-Analysis

Li Zhang¹, Guoqin Wu¹, Di Gao¹, Guijian Liu², Lin Pan¹, Liyan Ni³, Zheng Li⁴, Qiang Wang¹*

¹ Department of Dermatology, Zhongshan Hospital, Fudan University, Shanghai, P.R. China, ² Key Laboratory of Viral Heart Diseases, Ministry of Public Health, Shanghai Institute of Cardiovascular Diseases, Zhongshan Hospital, Fudan University, Shanghai, P.R. China, ³ Department of Dermatology, Shanghai Skin Diseases Hospital, Shanghai, P.R. China, ⁴ Department of Biomedical Research Center, Zhongshan Hospital, Fudan University, Shanghai, P.R. China

* wang.qiang@zs-hospital.sh.cn

Abstract

Objectives
Interstitial lung disease (ILD) is an extramuscular manifestation that results in increased morbidity and mortality from polymyositis (PM) and dermatomyositis (DM). The aim of this study was to systematically evaluate risk factors associated with the development of ILD in PM/DM.

Methods
Observational studies were identified from searching PubMed, Medline, Embase, and the Cochrane Library. Pooled odds ratios (ORs) or standardized mean differences (SMDs) and corresponding 95% confidence intervals (CIs) were obtained for the relationships between risk factors and ILD in PM/DM.

Results
Twenty-three studies were selected for a meta-analysis that included 834 patients and 1245 control subjects. Risk factors that may have increased the risk of developing ILD in PM/DM patients included older age at diagnosis (SMD, 0.35; 95% CI, 0.18–0.52; \( P < 0.0001 \)), arthritis/arthralgia (OR, 3.17; 95% CI, 1.99–5.04; \( P < 0.00001 \)), fever (OR, 2.31; 95% CI, 1.42–3.76; \( P = 0.0007 \)), presence of anti-Jo-1 antibodies (OR, 3.34; 95% CI, 2.16–5.16; \( P < 0.00001 \)), elevated erythrocyte sedimentation rate (ESR; SMD, 0.48; 95% CI, 0.32–0.64; \( P < 0.00001 \)), presence of anti-MDA5 antibodies (OR, 18.26; 95% CI, 9.66–34.51; \( P < 0.00001 \)), and elevated C-reactive protein level (CRP; OR, 3.50; 95% CI, 1.48–
8.28; \( P = 0.004 \)). Meanwhile, malignancy (OR, 0.36; 95% CI, 0.18–0.72; \( P = 0.004 \)) reduced the risk of developing ILD in PM/DM patients.

**Conclusion**

Our meta-analysis results suggest that the association between PM/DM and ILD may be due to such risk factors as older age at diagnosis, arthritis/arthralgia, fever, presence of anti-Jo-1 antibodies, elevated ESR, presence of anti-MDA5 antibodies, and elevated CRP level, while malignancy was associated with a reduced risk of developing ILD. Thus, these variables may be used to guide screening processes for ILD in patients with PM/DM.

**Introduction**

Idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of rare inflammatory systemic disorders with a complicated etiopathogenesis. Polymyositis (PM) and dermatomyositis (DM) are systemic inflammatory diseases with unknown etiologies and prognoses that are characterized by varying degrees of muscle inflammation. PM and DM share similar features, with the exception that DM involves a characteristic heliotrope skin rash and Gottron’s papules [1]. Interstitial lung disease (ILD) is an extramuscular manifestation that contributes to increased morbidity and mortality in PM/DM patients when it is present at admission [2]. ILD has been reported in 19.9% to 78% of PM/DM cases [3]. The most common patterns of myositis-associated ILD histology in lung biopsy include nonspecific interstitial pneumonia, general interstitial pneumonia, organizing pneumonia, diffuse alveolar damage, and lymphocytic interstitial pneumonia [4].

Although the incidence of ILD associated with PM/DM has increased, the underlying pathogenesis remains unknown. Many studies have focused on the components of the cellular immune system for inducing ILD in IIMs. In PM, CD8+ T cells, CD68+ cells, and TNF-\( \alpha \) cells are closely associated with muscular inflammation [5]. In contrast to DM, PM involves a significant increase in the number of CD4+ T cells and B cells in the perivascular areas of muscle tissue [6]. Moreover, in our recent research, we found that CD8+ T cells and CD68+ cells predominate in lung tissues in both PM and DM, which further confirms that the pathogenesis in lung tissues is similar between PM and DM, and might play a role in ILD development in PM/DM [7]. In the presence of ILD, bronchoalveolar lavage has consistently revealed lymphocytosis with a marked predominance of CD8+ T cells, which is associated with anti-Jo-1 autoantibody expression [8].

The quality of life of PM/DM patients is poor; hence, those at high risk of developing ILD should be promptly identified. Of the eight known anti-isoleucyl-tRNA synthetase antibodies, anti-Jo-1 antibody has been shown to be significantly associated with a high prevalence of myositis-related ILD, whereas anti-OJ antibody, anti-PL-12 antibody, and anti-KS antibody have been shown to confer the greatest risk of developing ILD in PM/DM patients [9]. Amyopathic DM (ADM) and clinical ADM (CADM) are defined as disorders that show typical skin manifestations of DM without evidence of clinical myositis [10]. The presence of anti-CADM-140 antibodies is implicated in individual mortality risk in DM patients with ILD. CADM patients, especially those positive for anti-MDA5 (melanoma differentiation-associated gene 5) antibodies, are known to develop acute, life-threatening, and progressive ILD frequently [11]. Some studies have shown that stereotypical clinical features, including age, fever, Raynaud’s phenomenon, and mechanic’s hands, increase the risk of developing ILD in PM/DM [12–14]. However,
previous studies that investigated such correlating factors of ILD in DM/PM patients were limited in size and had conflicting results [15]. In the present study, we identified risk factors for ILD in patients with PM/DM and performed a meta-analysis of published observational studies to assess these factors.

**Materials and Methods**

**Data Sources**

We identified all relevant studies on ILD associated with PM/DM published before January 1, 2016 that were listed in four international scientific databases: PubMed, Medline, Embase, and the Cochrane Library. Searches were restricted to articles written in English. The following keywords and text words were used: “myositis” OR “inflammatory myopathy” OR “polymyositis” OR “dermatomyositis” combined with “interstitial lung disease” OR “ILD”. Relevant references cited in the original articles were also reviewed.

**Study Selection and Data Extraction**

Studies had to meet the following eligibility criteria: (1) were retrospective studies with detailed information about the ILD status of PM and DM patients; (2) included cases in accordance with a probable or definitive diagnosis of PM or DM based on Bohan and Peter’s criteria [16,17]; (3) considered all types of ILD based on the American Thoracic Society and European Respiratory Society’s classification [18]; (4) included more than 20 subjects; (5) included sufficient information to calculate odds ratios (ORs) with 95% confidence intervals (CIs) and standardized mean differences (SMD) for the risk factors; and (5) included at least one potential risk factor.

Studies were excluded if (1) they were cadaveric or biomechanical studies, reviews, expert opinions, case reports, or letters that were not published in full; (2) they lacked a control group or provided data by comparing the difference in ILD between PM and DM (lacking a control group of PM/DM without ILD); or (3) it was impossible to extract relevant data from the outcomes. For studies that were conducted by the same research group with similar subjects, we prioritized the higher-quality study.

Two investigators (LZ and GQW) independently reviewed each retrieved article. Disagreement between the two reviewers was resolved by discussion and consensus. The senior investigator (QW) confirmed the final results. Information was extracted on the first author; publication year; geographical region of the population; study design; number of subjects enrolled; number of women; mean age at diagnosis, alanine aminotransferase (ALT) level, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) level; and the number of patients with Gottron’s sign, heliotrope rash, arthritis/arthritis, Raynaud’s phenomenon, dysphagia, malignancy, fever, antinuclear antibodies (ANAs), anti-Jo-1 antibodies, anti-MDA5 antibodies, and ILD. In addition, the quality of nonrandomized studies was assessed with the Newcastle-Ottawa scale for subject groups, comparability, and outcome. The selected studies were assigned a high, moderate, or low methodological quality with scores >6, 4–6, and <4, respectively (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).

**Data Analysis**

We combined trial results for estimating risk factors using Review Manager 5.3 (RevMan 2012, http://tech.cochrane.org/revman/). We presented results as summary ORs or SMDs with 95% CIs.
Between-study heterogeneity was tested with the Cochrane Q test and $I^2$ statistics. A $P$ value of $<0.05$ for the Cochrane Q test was considered to indicate significant heterogeneity. An $I^2$ value of $>50\%$ was considered to indicate significant heterogeneity. We used the random-effects model to calculate the ORs (or SMDs) and 95\% CIs [19]. Publication bias was estimated with the Begg’s and Egger’s tests. A $P$ value of $<0.05$ was considered statistically significant (Stata SE software, StataCorp, College Station, Texas).

**Results**

**Database Search**

In the initial search, 1152 studies were identified. All titles and abstracts were screened, and 163 potentially relevant full-text papers were selected. After a detailed review, 15 variables associated with PM/DM-associated ILD from 23 studies met the selection criteria and were included in the final analysis (Fig 1).

**Study Characteristics and Quality Assessment**

The 23 selected studies [13–15,20–39] included 2079 patients who fulfilled the inclusion criteria. Of these patients, there were 834 with ILD and 1245 without ILD, who were considered control subjects. The studies analyzed the following characteristics (geographical region of the study, matched variables analyzed, study quality based on the Newcastle-Ottawa Scale, study size, and percentage of patients with ILD), which are listed in Table 1.

**Heterogeneity Test**

No significant heterogeneity was observed for age at diagnosis ($P = 0.12, I^2 = 35\%$); proportion of women ($P = 0.74, I^2 = 0\%$); proportion of patients with Gottron’s sign ($P = 0.23, I^2 = 27\%$), heliotrope rash ($P = 0.08, I^2 = 50\%$), malignancy ($P = 0.49, I^2 = 0\%$), fever ($P = 0.18, I^2 = 33\%$), anti-Jo-1 antibodies ($P = 0.54, I^2 = 0\%$), or anti-MDA5 antibodies ($P = 0.98, I^2 = 0\%$); or levels of ALT ($P = 0.17, I^2 = 44\%$) or ESR ($P = 0.62, I^2 = 0\%$). Significant heterogeneity was observed for the proportion of patients with arthritis/arthralgia ($P = 0.01, I^2 = 53\%$), Raynaud’s phenomenon ($P = 0.03, I^2 = 59\%$), dysphagia ($P = 0.003, I^2 = 75\%$), and ANA ($P = 0.001, I^2 = 63\%$) (Table 2).

**Meta-analysis**

The random-effects model was applied for the meta-analysis based on the results of heterogeneity testing. The potential risk factors that were evaluated for their association with the development of ILD were as follows: (Table 2)

1. Demographic characteristics: age at diagnosis (SMD, 0.35; 95\% CI, 0.18–0.52; $P < 0.0001$) and female sex (OR, 0.94; 95\% CI, 0.72–1.23; $P = 0.65$). (Fig 2)

2. Clinical features: Gottron’s sign (OR, 0.93; 95\% CI, 0.63–1.38; $P = 0.73$), heliotrope rash (OR, 1.42; 95\% CI, 0.88–2.28; $P = 0.15$), arthritis/arthralgia (OR, 3.17; 95\% CI, 1.99–5.04; $P < 0.00001$), Raynaud’s phenomenon (OR, 1.62; 95\% CI, 0.69–3.84; $P = 0.27$), dysphagia (OR, 1.22; 95\% CI, 0.50–2.97; $P = 0.65$), malignancy (OR, 0.36; 95\% CI, 0.18–0.72; $P = 0.004$), and fever (OR, 2.31; 95\% CI, 1.42–3.76; $P = 0.0007$). (Fig 3)

3. Laboratory findings: Presence of ANA (OR, 0.89; 95\% CI, 0.56–1.40; $P = 0.60$), anti-Jo-1 antibodies (OR, 3.34; 95\% CI, 2.16–5.16; $P < 0.00001$), and anti-MDA5 antibodies (OR, 18.26; 95\% CI, 9.66–34.51; $P < 0.00001$); and levels of ALT (OR, 0.04; 95\% CI, −0.28 to
Our findings demonstrate that age at diagnosis; the presence of arthralgia/arthritis, malignancy, fever, anti-Jo-1 antibodies, and anti-MDA5 antibodies; and ESR and CRP levels were associated with ILD in patients with PM/DM (Figs 1–3). No associations were observed between ILD and female sex, Gottron’s sign, heliotrope rash, Raynaud’s phenomenon, dysphagia, presence of ANA, or ALT levels (S1–S3 Figs).

**Sensitivity Analysis**

We conducted a sensitivity analysis to determine the relationships between arthritis/arthralgia, Raynaud’s phenomenon, dysphagia, ANA, and risks of ILD. In order to identify possible sources of heterogeneity, the analyses were repeated by removing one study per iteration by using Stata SE. The overall significance of the pooled ORs or SMDs remained the same when
any single study was removed, except for Raynaud’s phenomenon. For Raynaud’s phenomenon, the OR derived from five studies was 1.10 (95% CI, 0.67–1.80), with the exception of the study by Xiaomin et al. [13]. For Raynaud’s phenomenon, we did not render the stable relationship between Raynaud’s phenomenon and ILD in PM/DM as conclusive (Fig 5).

**Publication Bias**

Publication bias of the included articles was examined. No significant publication bias was found by using Begg’s and Egger’s tests for age at diagnosis ($P = 0.876, P = 0.398$), female sex ($P = 1.000, P = 0.458$), Gottron’s sign ($P = 1.000, P = 0.871$), heliotrope rash ($P = 1.000, P = 0.942$), arthritis/arthritis, Raynaud’s phenomenon ($P = 0.451, P = 0.08$), dysphagia ($P = 1.000, P = 0.273$), malignancy ($P = 0.707, P = 0.271$), fever ($P = 1.000, P = 0.573$), ALT level

Table 1. Studies included in the meta-analysis.

| Study                     | Region       | Matched or adjusted variables analysed                                      | Quality | Study size (with ILD %) |
|---------------------------|--------------|-----------------------------------------------------------------------------|---------|-------------------------|
| E.H.Kang 2005 [20]        | Korea        | female sex, age, arthritis/arthritis, dysphagia, malignancy, ANA, anti-Jo-1 antibody | 7       | 72 (40.3%)              |
| Felix Chua 2012 [21]      | England      | female sex, age, anti-Jo-1 antibody, ANA, ESR                               | 7       | 107 (37.4%)             |
| Hao Wu 2013 [22]          | China        | age, Gottron’s sign, heliotrope rash, arthritis/arthritis, dysphagia, ANA, anti-Jo-1 antibody, ALT, ESR | 7       | 230 (49.6%)             |
| I.MARIE 2002 [15]         | France       | female sex, arthritis/arthritis, malignancy, ANA, anti-Jo-1 antibody        | 7       | 156 (23.1%)             |
| I-Jung chen 2009 [23]     | China        | female sex, heliotrope rash, Gottron’s sign, arthritis/arthritis, raynaud’s phenomenon, dysphagia, malignancy, ANA, anti-Jo-1 antibody, ALT | 7       | 151 (19.9%)             |
| Jin Won Huh 2007 [24]     | Korea        | age, female sex, fever, ANA, anti-Jo-1 antibody, ESR                        | 7       | 99 (33.3%)              |
| Ji Su-yun 2010 [25]       | China        | female sex, heliotrope rash, Gottron’s sign, arthritis/arthritis, raynaud’s phenomenon, dysphagia, fever, anti-Jo-1 antibody, ALT | 7       | 197 (35.0%)             |
| Kazuyoshi Ishigaski 2013 [26] | Japan       | age, female sex, arthritis/arthritis, fever, malignancy, ANA, anti-Jo-1 antibody | 7       | 39 (38.5%)              |
| M.Fathi 2012 [27]         | Sweden       | female sex, arthritis/arthritis, raynaud’s phenomenon, ANA, anti-Jo-1 antibody | 7       | 26 (23.1%)              |
| Takahisa Gono 2014 [28]   | Japan        | female sex, arthritis/arthritis, raynaud’s phenomenon, fever                | 7       | 38 (44.7%)              |
| Thomas J.Richards 2009 [29] | America  | arthritis/arthritis, raynaud’s phenomenon, fever                           | 6       | 90 (85.6%)              |
| Xiaomin Cen 2013 [13]     | China        | age, female sex, heliotrope rash, Gottron’s sign, arthritis/arthritis, raynaud’s phenomenon, fever, ANA, anti-Jo-1 antibody | 8       | 134 (61.9%)             |
| Yi Ju CHEN 2007 [14]      | China        | female sex, heliotrope rash, Gottron’s sign, arthritis/arthritis, dysphagia, fever, ANA, anti-Jo-1 antibody | 6       | 56 (75%)                |
| Yoshinaka Muro 2013 [30]  | Japan        | age, female sex, arthritis/arthritis, dysphagia, fever, ANA, anti-Jo-1 antibody | 6       | 25 (68%)                |
| Yuechi Sun 2013 [31]      | China        | female sex, heliotrope rash, Gottron’s sign, arthritis/arthritis, fever, ANA, anti-Jo-1 antibody, ALT | 7       | 41 (61.0%)              |
| Zhiyong Chen 2013 [32]    | China        | MDA5                                                                        | 6       | 64 (75%)                |
| Tomohiro Koga 2012 [33]   | Japan        | MDA5                                                                        | 7       | 79 (67.1%)              |
| Ran Nakashima 2010 [34]   | Japan        | MDA5                                                                        | 7       | 37 (67.6%)              |
| Kei Hoshino 2010 [35]     | Japan        | MDA5                                                                        | 7       | 61 (52.5%)              |
| John C. Hall 2013 [36]    | America      | MDA5                                                                        | 7       | 160 (15.6%)             |
| Moises Labrador-Horrillo 2014 [37] | Spain | MDA5 | 7 | 128 (8.6%) |
| Eun Ha Kang 2010 [38]     | Korea        | MDA5                                                                        | 7       | 49 (22.4%)              |
| Yu. X 2015 [39]           | China        | female sex, arthritis/arthritis, raynaud’s phenomenon, ANA, anti-Jo-1 antibody, MDA5 | 7       | 40 (27.5%)              |

doi:10.1371/journal.pone.0155381.t001
Table 2. Associations of PM/DM Associated ILD with Potential Factors In 23 Studies of 2079 Patients.

| Factors                             | Number of Studies | Number of Patients | OR/SMD[95%CI]          | Heterogeneity | Begg’s test(P) | Egger’s test(P) |
|-------------------------------------|-------------------|--------------------|------------------------|---------------|----------------|-----------------|
|                                     |                   |                    |                        |               |                |                 |
| Demographics                        |                   |                    |                        |               |                |                 |
|                                     |                   |                    |                        |               |                |                 |
| Age                                 | 11                | 1069               | SMD 0.35 [0.18, 0.52]   | 0.12          | 35             | 0.876           | 0.398           |
|                                     |                   |                    |                         |               |                |                 |                 |
| Female                              | 14                | 1181               | OR 0.94 [0.72, 1.23]    | 0.74          | 0              | 1.000           | 0.458           |
| Clinical features                   |                   |                    |                        |               |                |                 |                 |
| Gottron’s sign                      | 6                 | 809                | OR 0.93 [0.63, 1.38]    | 0.23          | 27             | 1.000           | 0.871           |
|                                     |                   |                    |                        |               |                |                 |                 |
| Heliotrope rash                     | 6                 | 809                | OR 1.42 [0.88, 2.28]    | 0.08          | 50             | 1.000           | 0.942           |
| Arthritis/ Arthralgia               | 12                | 1232               | OR 3.17 [1.99, 5.04]    | 0.01          | 53             | 0.451           | 0.08            |
|                                     |                   |                    |                        |               |                |                 |                 |
| Raynaud’s phenomenon                | 6                 | 638                | OR 1.62 [0.69, 3.84]    | 0.03          | 59             | 0.452           | 0.277           |
| Dysphagia                           | 5                 | 404                | OR 1.22 [0.50, 2.97]    | 0.003         | 75             | 1.000           | 0.273           |
| Fever                               | 7                 | 665                | OR 2.31 [1.42, 3.76]    | 0.18          | 33             | 0.089           | 0.270           |
|                                      |                   |                    |                        |               |                |                 |                 |
| Malignancy                          | 6                 | 507                | OR 0.36 [0.18, 0.72]    | 0.49          | 0              | 0.707           | 0.271           |
|                                     |                   |                    |                        |               |                |                 |                 |
| Laboratory tests                    |                   |                    |                        |               |                |                 |                 |
| ANA                                 | 13                | 1288               | OR 0.89 [0.56, 1.40]    | 0.001         | 63             | 0.059           | 0.022           |
|                                     |                   |                    |                        |               |                |                 |                 |
| Anti-Jo-1 antibodies                | 13                | 1128               | OR 3.34 [2.16, 5.16]    | 0.54          | 0              | 0.300           | 0.018           |
| ALT                                 | 3                 | 389                | SMD 0.04 [-0.28, 0.37]  | 0.17          | 44             | 1.000           | 0.919           |
| ESR                                 | 5                 | 674                | SMD 0.48 [0.32, 0.64]   | 0.62          | 0              | 0.462           | 0.182           |
| Anti-MDA5 antibody                  | 8                 | 618                | OR 18.26 [9.66, 34.51]  | 0.98          | 0              | 0.108           | 0.108           |
| CRP                                 | 2                 | 174                | OR 3.50 [1.48, 8.28]    | 0.26          | 23             | 1.000           |                  |

Discussion

To the best of our knowledge, this analysis is the first to demonstrate systematically the variables associated with the development of ILD in PM/DM patients. Disease progression is frequently aggressive and refractory for patients with PM or DM and is complicated when ILD is not recognized at an early stage [4]. However, little systematic evidence has yet shown a definitive relationship between the development of ILD and PM/DM.

A: Age

Table 2 shows the associations of PM/DM Associated ILD with potential factors in 23 studies of 2079 patients. The factors include demographics, clinical features, and laboratory tests. The table lists the number of studies, number of patients, odds ratio (OR) or standard mean difference (SMD), along with 95% confidence intervals (CI), heterogeneity tests, and potential publication bias tests.

**Factors Associated with Interstitial Lung Disease**

(P = 1.000, P = 0.919), ESR (P = 0.462, P = 0.182); or anti-MDA5 antibody (P = 0.108, P = 0.108; Table 2).

**Discussion**

To the best of our knowledge, this analysis is the first to demonstrate systematically the variables associated with the development of ILD in PM/DM patients. Disease progression is frequently aggressive and refractory for patients with PM or DM and is complicated when ILD is not recognized at an early stage [4]. However, little systematic evidence has yet shown a definitive relationship between the development of ILD and PM/DM.
### A: Heliotrope Rash

| Study or Subgroup | with ILD Events | without ILD Events | Total Events | Total Weight | M-H Random, 95% CI | Odds Ratio M-H Random, 95% CI |
|-------------------|-----------------|--------------------|--------------|--------------|---------------------|--------------------------------|
| Hao Wu 2013       | 52              | 114                | 37           | 116          | 24.5%               | 1.79 [1.05, 3.08]              |
| I-Jung chen 2009  | 6               | 30                 | 24           | 121          | 14.1%               | 0.64 [0.24, 1.70]              |
| Ji Su-yun 2010    | 41              | 69                 | 72           | 129          | 22.9%               | 1.14 [0.63, 2.08]              |
| Xiaomin Cen 2013  | 37              | 83                 | 10           | 51           | 17.3%               | 3.30 [1.46, 7.45]              |
| Yu Ju CHEN 2007   | 10              | 23                 | 17           | 33           | 12.6%               | 0.72 [0.25, 2.11]              |
| Yuechi Sun 2013   | 20              | 25                 | 10           | 16           | 8.6%                | 2.40 [0.59, 9.62]              |
| **Total (95% CI)**| **344**         | **465**            | **416**      | **180**      | **100.0%**          | **1.42 [0.88, 2.28]**          |

Total events: 168 / 180

Heterogeneity: Tau² = 0.16; Chi² = 9.92, df = 5 (P = 0.08); I² = 56%

Test for overall effect: Z = 1.45 (P = 0.15)

### B: Arthritis/Arthralgia

| Study or Subgroup | with ILD Events | without ILD Events | Total Events | Total Weight | M-H Random, 95% CI | Odds Ratio M-H Random, 95% CI |
|-------------------|-----------------|--------------------|--------------|--------------|---------------------|--------------------------------|
| E.H.Kang 2005     | 15              | 29                 | 12           | 43           | 9.7%                | 2.77 [1.03, 7.43]              |
| Hao Wu 2013       | 29              | 114                | 5            | 116          | 8.7%                | 7.57 [2.61, 20.39]             |
| I-Jung chen 2009  | 13              | 30                 | 28           | 121          | 11.0%               | 2.54 [1.10, 5.80]              |
| I.Marie 2002      | 24              | 36                 | 22           | 120          | 11.1%               | 9.91 [3.67, 24.49]             |
| Ji Su-yun 2010    | 32              | 69                 | 34           | 126          | 13.2%               | 2.39 [1.29, 4.42]              |
| Kazuyoshi Ishigasaki 2013 | 11 | 15                | 17           | 24           | 6.5%                | 1.13 [0.27, 4.80]              |
| M.Fathi 2012      | 5               | 6                  | 9            | 20           | 3.4%                | 6.11 [0.60, 62.23]             |
| Thomas J.Richards 2009 | 54 | 77                  | 11           | 13           | 5.7%                | 0.43 [0.09, 2.09]              |
| Xiaomin Cen 2013  | 45              | 83                 | 9            | 51           | 11.0%               | 5.62 [2.34, 12.79]             |
| Yu Ju CHEN 2007   | 14              | 23                 | 7            | 33           | 8.1%                | 5.78 [1.77, 18.85]             |
| Yu X 2015         | 1               | 11                 | 5            | 29           | 3.4%                | 0.48 [0.05, 4.65]              |
| Yuechi Sun 2013   | 17              | 25                 | 7            | 16           | 7.3%                | 2.73 [0.75, 9.99]              |
| **Total (95% CI)**| **518**         | **714**            | **580**      | **166**      | **100.0%**          | **3.17 [1.99, 5.04]**          |

Total events: 260 / 166

Heterogeneity: Tau² = 0.33; Chi² = 23.84, df = 11 (P = 0.01); I² = 53%

Test for overall effect: Z = 4.67 (P < 0.00001)

### C: Malignancy

| Study or Subgroup | with ILD Events | without ILD Events | Total Events | Total Weight | M-H Random, 95% CI | Odds Ratio M-H Random, 95% CI |
|-------------------|-----------------|--------------------|--------------|--------------|---------------------|--------------------------------|
| E.H.Kang 2005     | 2               | 29                 | 4            | 43           | 15.3%               | 0.72 [0.12, 4.23]              |
| I-Jung chen 2009  | 3               | 30                 | 21           | 121          | 29.1%               | 0.53 [0.15, 1.91]              |
| I.Marie 2002      | 2               | 36                 | 26           | 120          | 21.5%               | 0.21 [0.05, 0.84]              |
| Kazuyoshi Ishigasaki 2013 | 8 | 15                 | 9            | 16           | 5.4%                | 0.03 [0.00, 0.63]              |
| Yu Ju CHEN 2007   | 2               | 23                 | 8            | 33           | 17.5%               | 0.39 [0.06, 1.56]              |
| Yuechi Sun 2013   | 2               | 25                 | 2            | 16           | 11.2%               | 0.61 [0.08, 4.62]              |
| **Total (95% CI)**| **158**         | **349**            | **171**      | **89**       | **100.0%**          | **0.36 [0.10, 0.72]**          |

Total events: 11 / 89

Heterogeneity: Tau² = 0.00; Chi² = 4.40, df = 5 (P = 0.49); I² = 0%

Test for overall effect: Z = 2.89 (P = 0.004)

### D: Fever

| Study or Subgroup | with ILD Events | without ILD Events | Total Events | Total Weight | M-H Random, 95% CI | Odds Ratio M-H Random, 95% CI |
|-------------------|-----------------|--------------------|--------------|--------------|---------------------|--------------------------------|
| Ji Su-yun 2010    | 30              | 69                 | 18           | 128          | 23.8%               | 4.70 [2.36, 9.36]              |
| Jin Won Huh 2007  | 15              | 33                 | 17           | 86           | 18.3%               | 2.40 [1.00, 5.79]              |
| Kazuyoshi Ishigasaki 2013 | 8 | 25                 | 6            | 24           | 11.4%               | 1.41 [0.40, 4.92]              |
| Thomas J.Richards 2009 | 26 | 77                 | 3            | 13           | 9.8%                | 1.70 [0.43, 6.71]              |
| Xiaomin Cen 2013  | 36              | 83                 | 11           | 51           | 20.6%               | 2.79 [1.28, 6.21]              |
| Yu Ju CHEN 2007   | 14              | 23                 | 22           | 33           | 13.6%               | 0.78 [0.26, 2.35]              |
| Yuechi Sun 2013   | 3               | 24                 | 0            | 16           | 2.4%                | 5.37 [0.26, 111.39]            |
| **Total (95% CI)**| **334**         | **331**            | **330**      | **100.0%**   | **2.31 [1.42, 3.76]** |

Total events: 132 / 77

Heterogeneity: Tau² = 0.13; Chi² = 8.93, df = 6 (P = 0.19); I² = 33%

Test for overall effect: Z = 3.38 (P = 0.0007)

Fig 3. Forest plots generated by meta-analysis for the significant findings about clinical features from the studies. (A) heliotrope rash. (B) arthritis/arthralgia. (C) Malignancy. (D) fever.

doi:10.1371/journal.pone.0155381.g003
### A: Jo-1

| Study or Subgroup | with ILD | without ILD | Odds Ratio M.H. Random, 95% CI | Odds Ratio M.H. Random, 95% CI |
|-------------------|----------|-------------|------------------------------|------------------------------|
| E.H Kang 2005     | 6        | 22          | 20                            | 2.2%                         | 16.15 [0.85, 308.15] |
| Felix Chua 2012   | 10       | 36          | 6                             | 16.52%                       | 3.21 [0.05, 9.80]   |
| Hao Wu 2013       | 7        | 114         | 0                              | 2.3%                         | 16.26 [0.92, 299.05] |
| I.Jung chen 2009  | 6        | 24          | 2                              | 6.7%                         | 8.67 [1.80, 46.68]  |
| I.MARIE 2002      | 50       | 120         | 12                             | 36.9%                        | 1.97 [0.88, 4.43]   |
| Ji Su-yun 2010    | 5        | 48          | 2                              | 6.7%                         | 5.52 [1.03, 29.60]  |
| Jin Won Huh 2007  | 4        | 21          | 1                              | 28.3%                        | 6.35 [0.65, 61.73]  |
| Kazuyoshi Ishigaki 2013 | 5   | 15          | 5                              | 9.9%                         | 1.90 [0.44, 8.16]   |
| M.Fath 2012       | 3        | 6           | 2                              | 4.0%                         | 9.00 [1.03, 79.57]  |
| Xiaomin Cen 2013  | 17       | 83          | 3                              | 11.5%                        | 4.12 [1.14, 14.86]  |
| Yi Ju CHER 2007   | 5        | 23          | 1                              | 3.8%                         | 8.89 [0.96, 82.12]  |
| YuX 2015          | 0        | 11          | 3                              | 2.9%                         | 0.33 [0.02, 6.60]   |
| Yuechi Sun 2013   | 1        | 25          | 0                              | 1.8%                         | 2.02 [0.08, 52.68]  |

Total (95% CI) 548 | 580 | 100.0% | 3.34 [2.16, 5.16] |

Heterogeneity: Tau² = 0.00, Chi² = 10.86, df = 12 (P = 0.54), I² = 0%
Test for overall effect: Z = 5.43 (P < 0.00001)

### B: ESR

| Study or Subgroup | with ILD | without ILD | Std. Mean Difference M.H. Random, 95% CI |
|-------------------|----------|-------------|----------------------------------------|
| Felix Chua 2012   | 36.9     | 30.2        | 30.7                                  |
| Hao Wu 2013       | 26.9     | 18.1        | 14.7                                  |
| Ji Su-yun 2010    | 47.7     | 25.9        | 21.8                                  |
| Jin Won Huh 2007  | 54.13    | 28.7        | 25.4                                  |
| Yuechi Sun 2013   | 28.15    | 12.48       | 15.7                                  |

Total (95% CI) 281 | 393 | 100.0% | 0.48 [0.32, 0.64] |

Heterogeneity: Tau² = 0.00, Chi² = 2.84, df = 4 (P = 0.62), I² = 0%
Test for overall effect: Z = 5.99 (P < 0.00001)

### C: MDA5

| Study or Subgroup | with ILD | without ILD | Odds Ratio M.H. Random, 95% CI |
|-------------------|----------|-------------|------------------------------|
| Zhijong Chen 2013 | 28       | 48          | 16                            | 4.9%                         | 38.87 [2.21, 684.84] |
| Ran Nakashima 2010| 12       | 25          | 1                             | 8.4%                         | 10.15 [1.13, 90.94] |
| Kei Hoshino 2010  | 19       | 32          | 1                             | 9.1%                         | 40.92 [4.93, 339.48] |
| Tomohiro Koga 2012| 16       | 53          | 1                             | 9.3%                         | 10.91 [1.35, 86.80] |
| YuX 2015          | 8        | 11          | 4                             | 14.1%                        | 16.67 [3.08, 90.82] |
| Eun Ha Kang 2010  | 8        | 11          | 3                             | 14.5%                        | 14.00 [2.63, 74.59] |
| Moises Labrador-Horillo 2014 | 8 | 11 | 11 | 17 | 19.6% | |
| John C.Hall 2013  | 8        | 25          | 3                             | 20.1%                        | 20.71 [5.01, 85.84] |

Total (95% CI) 216 | 402 | 100.0% | 18.26 [9.66, 34.51] |

Heterogeneity: Tau² = 0.00, Chi² = 1.50, df = 7 (P = 0.98), I² = 0%
Test for overall effect: Z = 8.94 (P < 0.00001)

### D: CRP

| Study or Subgroup | with ILD | without ILD | Odds Ratio M.H. Random, 95% CI |
|-------------------|----------|-------------|------------------------------|
| Xiaomin Cen 2013  | 46       | 83          | 16                            | 75.1%                        | 2.72 [1.31, 5.66] |
| YuX 2015          | 6        | 11          | 4                             | 24.9%                        | 7.50 [1.53, 36.71] |

Total (95% CI) 94 | 80 | 100.0% | 3.50 [1.48, 8.28] |

Heterogeneity: Tau² = 0.12, Chi² = 1.29, df = 1 (P = 0.26), I² = 23%
Test for overall effect: Z = 2.85 (P = 0.004)

---

Fig 4. Forest plots generated by meta-analysis for the significant findings about lab tests from the studies. (A) anti-Jo-1 antibody. (B) ESR. (C) MDA5. (D) CRP.

doi:10.1371/journal.pone.0155381.g004
In this meta-analysis and systematic review, we examined the clinical features and laboratory outcomes that influence the development of ILD associated with PM or DM. For the final analysis, we included 23 studies involving 2079 cases. Our results showed that nine factors (age at diagnosis, heliotrope rash, arthritis/arthralgia, malignancy, fever, presence of anti-Jo-1 antibody, elevated ESR, presence of anti-MDA5 antibody, and elevated CRP level) were associated with the development of ILD in patients with PM or DM. Among these characteristics, all except malignancy increased the risk of developing ILD. The presence of an underlying malignancy was associated with a reduced risk of ILD in PM/DM patients. Based on the results of this meta-analysis, female sex, Gottron’s sign, Raynaud’s phenomenon, dysphagia, ANA, and ALT did not show statistically significant relationships with ILD.

Statistical heterogeneity is a consequence of a greater variation among studies than would be expected by chance alone. A sensitivity analysis was performed to calculate these results (including for arthritis/arthralgia, dysphagia, and ANA) and demonstrate their stability and reliability.

ILD is frequently identified as an early manifestation of PM/DM on high-resolution computed tomography (HRCT). Up to 78% of patients with ILD have some degree of interstitial inflammation and fibrosis [40]. HRCT findings compatible with ILD show ground-glass
attenuation, consolidation, or reticulation (i.e., intralobular reticular opacities, interlobular septal thickening, or nonseptal linear or plate-like opacity) [41]. Although many physicians are aware of the association between DM and ILD, screening practices are highly variable [42]. Pulmonary function tests (PFTs) are frequently used as a first-line screening modality, but physicians may be uncertain as to how to interpret results, when to repeat PFTs, when to obtain a chest CT, and when to refer patients to a pulmonary specialist for further care. Identifying patients in high-risk groups based on their risk factors at the time of diagnosis in order to provide better management is essential, and many clinical research studies have been conducted to elucidate the clinical features and prognostic factors of these patients [42–44].

Arthritis/arthralgia and anti-Jo-1 antibody have long been known as potential predictors of the development of ILD in patients with PM/DM [15,45]. Antisynthetase syndrome is characterized by PM/DM with the presence of antisynthetase antibodies, fever, arthritis, Raynaud’s phenomenon, mechanic’s hands, and ILD. Among the antisynthetase antibodies, anti-Jo-1 antibody is the most common (60%–80%) [46]. In anti-Jo-1 antibody-positive individuals, the most striking feature is the extraordinarily high incidence of ILD, which has been shown to approach 90%[29]. In PM/DM with ILD, serum CRP and the interferon (IFN)-γ-inducible chemokines CXC motif- ligand 9 (CXCL9) and CXCL10 seemed to be associated with anti-Jo-1 antibody expression, which is associated with ILD [29]. Immune complexes have been suggested to induce endogenous IFN in anti-Jo-1- or anti-Ro 52/anti-Ro 60-antibody-positive IIM patients [47]. ILD in myositis is an important extramuscular manifestation of the presence of anti-Jo-1 antibody (an RNA-binding protein) in patients. IFN induction could play a role in the pathogenesis of ILD, as its interference is confined to the IgG fraction and the RNA from necrotic cells [47]. Sy et al. [25] reported the results of a retrospective multivariate analysis that revealed older age at onset, fever, and arthritis/arthralgia as independent factors associated with ILD in PM/DM (after excluding anti-Jo-1 antibody). In that retrospective study, arthritis/arthralgia (OR, 2.274; 95% CI, 1.101–4.695; P = 0.026) was the predictor of ILD in PM/DM patients. Based on general data, fever was more apparent in patients with ILD-associated myositis than in those without ILD, in accordance with our results. Age at diagnosis (especially >45 years) was reported to be an important factor associated with poor prognosis [15,23,48]. Our analysis revealed that older age at diagnosis was associated with an increased risk of ILD. In addition, a higher ESR level was significantly more frequent in IIM patients with ILD, suggesting that patients with ILD have more severe systemic inflammation [13,15,24,31]. Thus, a high level of ESR was associated with ILD in PM/DM. Malignancy is another complication of IIM. The prevalence of malignancy has been shown to be lower in patients with ILD than in those without ILD [15], similar to the results of our analysis, in which malignancy was associated with a reduced risk of ILD in patients with PM/DM. High levels of serum ferritin, ALT, aspartate aminotransferase, creatine kinase, and lactate dehydrogenase have been reported as indicators of ILD in CADM patients [31]. However, our analysis revealed that ALT was not a predictor of PM/DM-ILD. Dermatological manifestations, such as heliotrope rash and Gottron’s sign, were common phenomena in DM patients [13]. However, in our analysis, these phenomena were not associated with the development of ILD in PM/DM.

Anti-MDA5 antibody expression has been reported to be found specifically in CADM patients and to predict acute progressive ILD with a poor prognosis [34]. Thus, anti-MDA5 antibody may act as a specific biomarker for a subset of DM and acute ILD patients [49]. MDA5 has been shown to have an analytical sensitivity of 85% and an analytical specificity of 100%, and was useful for identifying patients with CADM or rapidly progressive ILD [50]. In addition, a major histocompatibility complex has long been recognized as a major genetic region associated with DM [51]. An interaction between HLA-DRB1 ‘03 and smoking was hypothesized for the formation of anti-Jo-1 antibody in IIM patients [52]. Furthermore, the
HLA-DRB1*03-DQA1*05-DQB1*02 haplotype was associated with the expression of the ILD phenotype in both DM and PM when associated with a positive antisynthetase antibody [52,53]. This line of inquiry deserves further research to investigate the importance of MDA5 and genetic predispositions in predicting ILD in PM/DM. In our analysis, MDA5 expression was confirmed as a factor associated with ILD in PM/DM.

Recently, some promising biomarkers, such as Krebs von den Lungen-6 (KL-6) and serum surfactant protein D (SP-D) level, have been reported to be used in the diagnosis of ILD in PM/DM. Moreover, ethnicity was shown to be as a risk factor of IIM-ILD in a cohort study [21]. More clinical studies need to assess the potential value of these new biomarkers, as well as that of ethnicity.

Our study has limitations. The number of patients enrolled, PM/DM disease duration, population distribution, and extent of the relationship between ILD and PM/DM varied across studies. Some publication bias was observed in Begg’s and Egger’s test plots for anti-Jo-1 antibody, ANA, and CRP. Positive results that showed significant findings were more easily published than were negative or inconclusive results. Although the total number of studies included was not small, more studies, especially prospective studies with large sample sizes, are still needed to investigate the potential relationship between these factors and ILD in PM/DM. Other factors contributing to heterogeneity may have been unidentified in our review. The shortage of retrospective trials on this topic is a limitation, and more cohort or retrospective case-control studies are needed to better understand the variables associated with ILD in PM/DM.

In summary, this is the first comprehensive systematic review and meta-analysis that evaluated all factors presumed to be associated with ILD in PM/DM patients. The factors that were found to increase the risk of ILD associated with PM and DM significantly include age at diagnosis, presence of heliotrope rash, presence of arthritis/arthritis, presence of fever, presence of anti-Jo-1 antibody, elevated ESR, presence of anti-MDA5 antibody, and elevated CRP level. Malignancy was associated with a reduced risk of ILD in PM/DM. Overall, our results are statistically robust, and the findings not only shed light on the clinical prognostic indicators of ILD in DM and PM but also demonstrate the potential pathogenesis associated with the disorders.

**Supporting Information**

S1 Fig. Forest plots generated by meta-analysis for the insignificant findings about demographics from the studies. (A) female sex.

(TIF)

S2 Fig. Forest plots generated by meta-analysis for the insignificant findings about clinical features from the studies. (A) Gottron’s sign. (B) Raynaud’s phenomenon. (C) dysphagia.

(TIF)

S3 Fig. Forest plots generated by meta-analysis for the insignificant findings about lab tests from the studies. (A) ANA. (B) ALT.

(TIF)

S1 PRISMA Checklist. PRISMA Checklist.

(DOC)

**Acknowledgments**

The authors have declared no conflicts of interest.
Author Contributions
Conceived and designed the experiments: QW LZ. Performed the experiments: GQW DG ZL. Analyzed the data: GJL LP LYN. Wrote the paper: QW LZ.

References
1. Troyanov Y, Targoff IN, Payette MP, Raynauld JP, Chartier S, Goulet JR, et al. (2014) Redefining dermatomyositis: a description of new diagnostic criteria that differentiate pure dermatomyositis from overlap myositis with dermatomyositis features. Medicine (Baltimore) 93: 318–332.
2. Marie I, Hatron PY, Dominique S, Cherin P, Mouthon L, Menard JF (2011) Short-term and long-term outcomes of interstitial lung disease in polymyositis and dermatomyositis: a series of 107 patients. Arthritis Rheum 63: 3439–3447. doi: 10.1002/art.30513 PMID: 21702020
3. Hallowell RW, Ascherman DP, Danoff SK (2014) Pulmonary manifestations of polymyositis/dermatomyositis. Semin Respir Crit Care Med 35: 239–248. doi:10.1055/s-0034-1371528 PMID: 24668538
4. Connors GR, Christopher-Stine L, Oddis CV, Danoff SK (2010) Interstitial lung disease associated with the idiopathic inflammatory myopathies: what progress has been made in the past 35 years? Chest 138: 1464–1474. doi: 10.1378/chest.10-0180 PMID: 21138882
5. Feng Y, Ni L, Wang Q (2013) Administration of cathepsin B inhibitor CA-074Me reduces inflammation and apoptosis in polymyositis. J Dermatol Sci 72: 158–167. doi: 10.1016/j.jdermsci.2013.06.014 PMID: 23890703
6. Reed AM, Ernste F (2009) The inflammatory milieu in idiopathic inflammatory myositis. Curr Rheumatol Rep 11: 295–301. PMID: 19691933
7. Zhang L, Fu XH, Yu Y, Shui RH, Li C, Zeng HY, et al. (2015) Treatment with CA-074Me, a Cathepsin B inhibitor, reduces lung interstitial inflammation and fibrosis in a rat model of polymyositis. Lab Invest 95: 65–77. doi: 10.1038/labinvest.2014.135 PMID: 25384123
8. Sauty A, Rochat T, Schoch OD, Hamacher J, Kurt AM, Dayer JM, et al. (1997) Pulmonary fibrosis with predominant CD8 lymphocytic alveolitis and anti-Jo-1 antibodies. Eur Respir J 10: 2907–2912. PMID: 9493684
9. Mimori T, Nakashima R, Hosono Y (2012) Interstitial lung disease in myositis: clinical subsets, biomarkers, and treatment. Curr Rheumatol Rep 14: 264–274. doi:10.1007/s11926-012-0246-6 PMID: 22367479
10. Gerami P, Schope JM, McDonald L, Walling HW, Sontheimer RD (2006) A systematic review of adult-onset clinically amyopathic dermatomyositis (dermatomyositis sine myositis): a missing link within the spectrum of the idiopathic inflammatory myopathies. J Am Acad Dermatol 54: 597–613. PMID: 16546580
11. Mukae H, Ishimoto H, Sakamoto N, Hara S, Kakugawa T, Nakayama S, et al. (2009) Clinical differences between interstitial lung disease associated with clinically amyopathic dermatomyositis and classic dermatomyositis. Chest 136: 1341–1347. doi:10.1378/chest.08-2740 PMID: 19581351
12. Targoff IN (1993) Humoral immunity in polymyositis/dermatomyositis. J Invest Dermatol 100: 116S–123S. PMID: 8423380
13. Chen YJ, Wu CY, Shen JL (2007) Predicting factors of interstitial lung disease in dermatomyositis and polymyositis. Acta Derm Venereol 87: 33–38. PMID: 17225013
14. American Thoracic S, European Respiratory S (2002) American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors. June 2001 and by the ERS Executive Committee, June 2001. Am J Respir Crit Care Med 165: 277–304. PMID: 11790668
15. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7: 177–188. PMID: 3802833
Factors Associated with Interstitial Lung Disease

20. Kang EH, Lee EB, Shin KC, Im CH, Chung DH, Han SK, et al. (2005) Interstitial lung disease in patients with polymyositis, dermatomyositis and amyopathic dermatomyositis. Rheumatology (Oxford) 44: 1282–1286.

21. Chua F, Higton AM, Colebatch AN, O’Reilly K, Grubnic S, Vlahos I, et al. (2012) Idiopathic inflammatory myositis-associated interstitial lung disease: ethnicity differences and lung function trends in a British cohort. Rheumatology (Oxford) 51: 1870–1876.

22. Wu H, Geng D, Xu J (2013) An approach to the development of interstitial lung disease in dermatomyositis: a study of 230 cases in China. J Int Med Res 41: 493–501. doi: 10.1177/0300067013476435 PMID: 23569020

23. Chen IJ, Jan Wu YJ, Lin CW, Fan KW, Luo SF, Ho HH, et al. (2009) Interstitial lung disease in polymyositis and dermatomyositis. Clin Rheumatol 28: 639–646. doi: 10.1007/s10067-009-1110-6 PMID: 19247576

24. Won Huh J, Soon Kim D, Keun Lee C, Yoo B, Bum Seo J, Kitaichi M, et al. (2007) Two distinct clinical types of interstitial lung disease associated with polymyositis-dermatomyositis. Respir Med 101: 1761–1769. PMID: 17428649

25. Ji SY, Zeng FQ, Guo Q, Tan GZ, Tang HF, Luo YJ, et al. (2010) Predictive factors and unfavourable prognostic factors of interstitial lung disease in patients with polymyositis or dermatomyositis: a retrospective study. Chin Med J (Engl) 123: 517–522.

26. Ishigaki K, Maruyama J, Hagino N, Murota A, Takizawa Y, Nakashima R, et al. (2013) Skin ulcer is a predictive and prognostic factor of acute or subacute interstitial lung disease in dermatomyositis. Rheumatol Int 33: 2381–2389. doi: 10.1007/s00296-013-2735-y PMID: 23553518

27. Fathi M, Barbasso Helmers S, Lundberg IE (2012) KL-6: a serological biomarker for interstitial lung disease in patients with polymyositis and dermatomyositis. J Intern Med 271: 589–597. doi: 10.1111/j.1365-2769.2011.02459.x PMID: 21950266

28. Gono T, Kaneho K, Kawaguchi Y, Hanaoka M, Kataoka S, Kuwana M, et al. (2014) Cytokine profiles in polymyositis and dermatomyositis complicated by rapidly progressive or chronic interstitial lung disease. Rheumatology (Oxford) 53: 2196–2203.

29. Richards TJ, Eggebeen A, Gibson K, Yousem S, Fuhrman C, Gochuico BR, et al. (2009) Characterization and peripheral blood biomarker assessment of anti-Jo-1 antibody-positive interstitial lung disease. Arthritis Rheum 60: 2183–2192. doi: 10.1002/art.24631 PMID: 19565490

30. Muro Y, Sugiyama K, Akiyama M (2013) Limitations of a single-point evaluation of anti-MDA5 antibody, ferritin, and IL-18 in predicting the prognosis of interstitial lung disease with anti-MDA5 antibody-positive dermatomyositis. Clin Rheumatol 32: 395–398. doi: 10.1007/s10067-012-2142-x PMID: 23250474

31. Sun Y, Liu Y, Yan B, Shi G (2013) Interstitial lung disease in clinically amyopathic dermatomyositis (CADM) patients: a retrospective study of 41 Chinese Han patients. Rheumatol Int 33: 1295–1302. doi: 10.1007/s00296-012-2545-7 PMID: 23143553

32. Chen Z, Cao M, Plana MN, Liang J, Cai H, Kuwana M, et al. (2013) 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 (Hoboken) 65: 1316–1324.

33. Koga T, Fujikawa K, Horai Y, Okada A, Kawashiri SY, Iwamoto N, et al. (2012) The diagnostic utility of anti-melanoma differentiation-associated gene 5 antibody testing for predicting the prognosis of Japanese patients with DM. Rheumatology (Oxford) 51: 1278–1284.

34. Nakashima R, Imura Y, Kobayashi S, Yukawa N, Yoshifuji H, Nojima T, et al. (2010) The RIG-I-like receptor IFIH1/MDA5 is a dermatomyositis-specific autoantigen identified by the anti-CADM-140 antibody. Rheumatology (Oxford) 49: 433–440.

35. Hoshino K, Muro Y, Sugiyama K, Tomita Y, Nakashima R, Mimori T (2010) Anti-MDA5 and anti-TIF1-gamma antibodies have clinical significance for patients with dermatomyositis. Rheumatol Int 30: 398. doi:10.1007/s10067-012-2192. doi:10.1007/s10067-009-1110-6 PMID: 21950266

36. Hall JC, Casciola-Rosen L, Samedy LA, Werner J, Owoyemi K, Danoff SK, et al. (2013) Anti-melanoma differentiation-associated protein 5-associated dermatomyositis: expanding the clinical spectrum. Arthritis Care Res (Hoboken) 65: 1307–1315.

37. Labrador-Horrillo M, Martinez MA, Selva-O’Callaghan A, Traller-Araguas E, Balada E, Vilardell-Tarres M, et al. (2014) Anti-MDA5 antibodies in a large Mediterranean population of adults with dermatomyositis. J Immunol Res 2014: 290797. doi: 10.1155/2014/290797 PMID: 24741593

38. Kang EH, Nakashima R, Mimori T, Kim J, Lee YJ, Lee EB, et al. (2010) Myositis autoantibodies in Korean patients with inflammatory myositis: anti-140-kDa polyepitope antibody is primarily associated with rapidly progressive interstitial lung disease independent of clinically amyopathic dermatomyositis. BMC Musculoskelet Disord 11: 223. doi: 10.1186/1471-2474-11-223 PMID: 20875136
39. Xu Y, Yang CS, Li YJ, Liu XD, Wang JN, Zhao Q, et al. (2015) Predictive factors of rapidly progressive-interstitial lung disease in patients with clinically amyopathic dermatomyositis. Clin Rheumatol.

40. Fathi M, Vikgren J, Boijsen M, Tylen U, Jorfeldt L, Torling G, et al. (2008) Interstitial lung disease in polymyositis and dermatomyositis: longitudinal evaluation by pulmonary function and radiology. Arthritis Rheum 59: 677–685. doi: 10.1002/art.23571 PMID: 18438901

41. Tanizawa K, Handa T, Nakashima R, Kubo T, Hosono Y, Aihara K, et al. (2013) The prognostic value of HRCT in myositis-associated interstitial lung disease. Respir Med 107: 745–752. doi: 10.1016/j.rmed.2013.01.014 PMID: 2345997

42. Fischer A, du Bois R (2012) Interstitial lung disease in connective tissue disorders. Lancet 380: 689–698. doi: 10.1016/S0140-6736(12)61079-4 PMID: 22901890

43. Fujisawa T, Hozumi H, Kono M, Enomoto N, Hashimoto D, Nakamura Y, et al. (2014) Prognostic factors for myositis-associated interstitial lung disease. PLoS One 9: e98824. doi: 10.1371/journal.pone.0098824 PMID: 24905449

44. Vij R, Strek ME (2013) Diagnosis and treatment of connective tissue disease-associated interstitial lung disease. Chest 143: 814–824. doi: 10.1378/chest.12-0741 PMID: 23460159

45. Danko K, Pomyi A, Constantin T, Borgulya G, Szegedi G (2004) Long-term survival of patients with idiopathic inflammatory myopathies according to clinical features: a longitudinal study of 162 cases. Medicine (Baltimore) 83: 35–42.

46. Marie I, Josse S, Decaux O, Dominique S, Diet E, Landron C, et al. (2012) Comparison of long-term outcome between anti-Jo1 and anti-PL7/PL12 positive patients with antisynthetase syndrome. Autoimmun Rev 11: 739–745. doi: 10.1016/j.autrev.2012.01.006 PMID: 22326685

47. Eloranta ML, Barbasso Helmers S, Ulfgren AK, Ronnblom L, Alm GV, Lundberg IE. (2007) A possible mechanism for endogenous activation of the type I interferon system in myositis patients with anti-Jo-1 or anti-Ro 52/anti-Ro 60 autoantibodies. Arthritis Rheum 56: 3112–3124. PMID: 17763410

48. Marie I, Hachulla E, Hatron PY, Hellot MF, Levesque H, Devulder B, et al. (2001) Polymyositis and dermatomyositis: short term and long-term outcome, and predictive factors of prognosis. J Rheumatol 28: 2230–2237. PMID: 11669162

49. Sato S, Hirakata M, Kawanaka M, Suwa A, Inada S, Mimori T, et al. (2005) Autoantibodies to a 140-kd polypeptide, CADM-140, in Japanese patients with clinically amyopathic dermatomyositis. Arthritis Rheum 52: 1571–1576. PMID: 15880816

50. Sato S, Hoshino K, Satoh T, Fujita T, Kawakami Y, Fujita T, et al. (2009) 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 60: 2193–2200. doi: 10.1002/art.24621 PMID: 19565506

51. Miller FW, Cooper RG, Vencovsky J, Rider LG, Danko K, Wedderburn LR, et al. (2013) Genome-wide association study of dermatomyositis reveals genetic overlap with other autoimmune disorders. Arthritis Rheum 65: 3239–3247. doi: 10.1002/art.38137 PMID: 23983088

52. Chinoy H, Adimulam S, Marriage F, New P, Vincze M, Zilahi E, et al. (2012) Interaction of HLA-DRB1*03 and smoking for the development of anti-Jo-1 antibodies in adult idiopathic inflammatory myopathies: a European-wide case study. Ann Rheum Dis 71: 961–965. doi: 10.1136/annrheumdis-2011-200182 PMID: 22186711

53. Chinoy H, Salway F, Fertig N, Shephard N, Tail BD, Wendy T, et al. (2006) In adult onset myositis, the presence of interstitial lung disease and myositis specific/associated antibodies are governed by HLA class II haplotype, rather than by myositis subtype. Arthritis Res Ther 8: R13. PMID: 16507114