Characterisation of Disease Patterns of Dermatomyositis with Different Initial Manifestations

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Research

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Abstract

Objectives

To study the characteristics and prognosis of dermatomyositis (DM) with different initial symptoms.

Patients and methods:

A retrospective analysis was performed on the patients who were first diagnosed with DM from 1 Jan. 2019 to 1 Jan. 2021. According to different initial symptoms, patients were divided into five groups, including rash, myasthenia, arthritis, respiratory symptom and atypical symptom group. Clinical and laboratory data were recorded. All patients were followed up until 31st May 2021.

Results

In total 136 patients, rash (40%) was the most common initial symptoms of DM, followed by respiratory symptoms (22%), arthritis (20%), muscle weakness (10%) and atypical symptoms (8%). Rash groups and atypical groups had a higher positive rate of anti-TIF1γ antibodies than arthritis groups and respiratory symptom groups ($P < 0.05$). Respiratory symptom and arthritis groups had a higher positive rate of anti-Ro52 antibodies than rash and myasthenia groups ($P < 0.05$). Respiratory groups had a higher incidence of ILD than rash and atypical groups. The FVC and DLCO in respiratory group were significantly lower than rash, arthritis and atypical groups ($P < 0.05$). The 3-year survival rate of rash groups was significantly higher than myasthenia groups and arthritis groups ($P < 0.05$).

Conclusions

DM patients with different initial manifestations had different pulmonary function tests, myositis antibodies and prognosis.

1. Introduction

As the most common type of idiopathic inflammatory myositis (IIM), dermatomyositis (DM) is a systemic autoimmune disease characterized by skin lesions and muscle inflammation, and the incidence of DM is approximately 1-6 per 100,000 individuals[1]. The pathogenesis of DM is multifaceted with the involvement of various factors including genetic, environmental, immunological, etc. Therefore, it has a protean clinical manifestation and prognosis [2, 3].

Rash was the most common initial symptom of DM[4]. Pathognomonic cutaneous lesions include heliotrope sign, Gottron papules and Gottron sign. Other manifestations include “V” sign, “shawl” sign, “holster” sign, nail-fold changes, and scalp involvement [1], clinically psoriasiform [5], mechanic hand,

panniculitis and calcinosis. Ulcerative lesions and panniculitis are more common in differentiation-associated protein 5 (MDA5) positive patients [6, 7]. Typical muscle involvements manifested as symmetric and proximal myasthenia. However, classic cutaneous and muscle involvements do not always coexist. Clinical amyopathic dermatomyositis (CADM) and clinical dermatomyositis sine dermatitis (DMSD) are two special types of DM. About 20% of DM was CADM [8] and 8% was DMSD [9]. In addition to skin and muscle, other organs or tissues may be afflicted including pulmonary, gastrointestinal, cardiac, renal, joint involvements. The incidence of malignancy is higher compared to healthy population. Interstitial lung disease (ILD) is the most common type of pulmonary involvement and is leading cause of mortality in DM patients. Because of protean manifestations, differential diagnosis is important in the first stage of the disease. Autoimmune diseases with different initial symptoms may have different clinical features. It has been reported that pulmonary complications were more progressive and severe in non-sicca onset patients than sicca onset patients[10]. The DM patients with ILD as an initial manifestation had lower incidences of heliotrope rash, chest V area rash, shawl sign and joint involvement[11], but the characteristics and prognosis of other initial symptom subgroups are not completely clear. Early diagnosis is a prerequisite for inducing remission and preventing sequelae[12]. In this report, we divided all the patients into five groups including rash, myasthenia, arthritis, respiratory symptom groups and atypical symptom groups according to the various initial symptoms. Subsequently, the characteristics and prognosis of DM were analyzed and clarified, which further facilitates clinicians with a better evaluation and management of DM patients.

2. Materials And Methods

2.1 A total of 136 cases of patients with first diagnosis of DM were collected from 1st Jan. 2019 to 1st Jan. 2021. Patients with different initial symptoms were divided into these five groups: rash groups, myasthenia groups, arthritis groups, respiratory symptoms groups and atypical symptoms groups. All patients were followed up until 31st May 2021. The research was conducted in accordance with the ethical standards of the Declaration of Helsinki and approved by ethics committee, and obtained informed consent of participants.

2.2 Inclusion criteria:

(1) Over 18 years old.

(2) Patients who met Bohan & Peter's criteria [13, 14] and 2020 ENMC classification criteria [15] , and were first diagnosed with DM.

(3) Complete basic information such as clinical features, laboratory examinations.

Exclusion criteria:

(1) Did not meet the above inclusion criteria;

(2) Other connective tissue diseases were excluded (rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, scleroderma, etc.)

(3) Excluded other serious diseases (cardiopulmonary failure, hepatic and renal dysfunction, serious cardiovascular, cerebrovascular diseases, etc.)

2.3 Data collection:

(1) Clinical features laboratory data, myositis antibodies and pulmonary function tests (PFTs) were obtained from inpatient medical records. The results of PFTs were showed as percentages of the predicted values of each parameter and corrected for age, gender, and height. Diffusion capacity of the lung for carbon (DLCO) ≥80% was defined as normal lung diffusion function. The percentage of forced vital capacity (FVC) ≥ 80% of predicted values, and/or the percentage of forced expiratory volume in 1s (FEV1) to the expected value ≥ 80%, and/or FEV1/FVC ≥ 92% were defined as normal lung function.

(2) Follow-up: The survival condition of all 136 patients were recorded from onset to 31st May 2021 through querying outpatient and inpatient medical records and telephone return visit. Overall survival was defined from time of onset to date of death or follow-up end time (31st May 2021).

2.4 Statistical analysis

SPSS (Version 25) was used for statistical analysis. Qualitative variables were presented as counts (n) and percentages (%) and chi-square tests or Fisher's Exact tests were used to establish statistical differences between groups. Quantitative variables were presented as median (P25, P75) by Kruskal-Wallis tests when normally distributed, and presented as mean ± standard deviation (SD) by one-way analysis of variance (ANOVA) when non-normally distributed. Kaplan-Meier analysis was used for survival analysis among subgroups, and the survival rate was compared by Log-rank test. $P < 0.05$ was considered statistically significant.

3. Results

Tables 1 to 4 summarized the characteristics and study results of all 136 patients. Among them, 99 (73%) patients were female and 37 (27%) were male. 78 (57%) patients were diagnosed between the ages of 40 and 60. 72 patients were recorded whether felt itch or not during the disease. Rash (n=55, 40%) was the most common first symptoms of DM, followed by respiratory symptom (n=30, 22%), arthritis (n=27, 20%), myasthenia (n=13, 10%), and atypical symptom (n =11, 8%). Atypical symptom included fever (n=7), diarrhea (n=2), dysphagia (n=1) and oral ulcer (n=1).

3.1 General features

The comparison of general features by clinical subgroups was shown in Table 1. The female to male ratio was about 2.7:1 in total patients. 43% (31/72) patients experienced itchy skin during the disease. There were no significant differences in gender, age, BMI, delay in diagnosis, smoking and itch

($P > 0.05$). The incidence of ILD in respiratory symptom groups was the higher than rash groups and atypical groups (100% *vs* 60%, 100% *vs* 54.4%, $P < 0.05$).

Table 1. General features in different subgroups of DM

Factors	Rash (N=55)	Myasthenia (N=13)	Arthritis (N=27)	Respiratory (N=30)	Atypical (N=11)	Test statistic	*P*
Gender, female (%)	41 (74.5)	8 (61.5)	21 (77.8)	22 (73.3)	7 (63.6)	1.726	0.796
Age(year)	47 (39, 61)	48 (39, 56)	50 (39, 54)	53 (47, 57)	63 (46, 65)	5.679	0.224
Delay in diagnosis (months)	3.5 (2.0, 6.3)	5 (2.5, 9.5)	3 (2, 9)	3 (2, 5)	2 (1, 4)	4.158	0.385
BMI (kg/m^2)	23.7 (21.8, 26.2)	23.0 (19.3, 25.9)	23.4 (20.8, 25.4)	25.5 (21.7, 26.6)	22.5 (21.7, 26.7)	2.975	0.562
Smoking (%)	5 (9.1)	1 (7.7)	1 (3.7)	2 (6.7)	2 (18.2)	2.522	0.637
ILD (%)	33 (60.0) a	10 (76.9) ab	21 (77.8) ab	30 (100.0) b	6 (54.4) a	18.337	0.001
Itch (%) #	17 (17/31, 54.8)	3 (3/5, 60.0)	5 (5/13, 38.5)	5 (5/18, 27.8)	1 (1/5, 20.0)	5.096	0.273

BMI = Body Mass Index, ILD = interstitial lung disease.

Note: # 72 patients were recorded whether felt itch or not during the disease. Qualitative variables were presented as counts (n) and percentages (%) by chi-square test or Fisher's Exact test. Values with letters a, b and significantly different across columns with Bonferroni's comparison tests ($P < 0.05$). Quantitative variables were presented as median (P25, P75) By Kruskal-Wallis test.

3.2 Laboratory indicators

serological indicators

We examined the serological indicators in these five groups (Table 2). There were differences in the distribution of TG in the DM subgroups by Kruskal-Wallis tests ($P = 0.029$), but no statistic difference was found in pairwise comparison with Bonferroni's multiple tests. The differences in other serological indicators among different subgroups were no statistical significance ($P > 0.05$).

Table 2. Serological indicators in different subgroups of DM

Factors	Rash (N=55)	Myasthenia (N=13)	Arthritis (N=27)	Respiratory (N=30)	Atypical (N=11)	Test statistic	*P*
CK (U/L)	63 (42, 230)	94 (48, 168)	31 (23, 87)	68 (39, 119)	86 (27, 185)	8.838	0.065
LDH (U/L)	344 (261, 476)	370 (320, 457)	297 (254, 350)	369 (269, 460)	321 (268, 418)	6.236	0.182
TC (mmol/L)	4.1 (3.6, 5.1)	5.1 (4.1, 5.9)	4.0 (3.5, 5.0)	4.3 (3.9, 5.3)	3.7 (3.3, 4.5)	8.934	0.063
TG (mmol/L)	1.6 (1.1, 2.1)	2.5 (1.5, 5.4)	2.2 (1.5, 3.2)	1.7 (1.3, 2.3)	1.2 (1.0, 1.7)	10.776	0.029
HDL (mmol/L)	1.1 ±0.4	1.0 ±0.3	1.0 ±0.3	1.0 ±0.3	0.9 ±0.1	1.805	0.132
LDL (mmol/L)	2.6 ±0.9	2.9 ±0.7	2.5 ±1.0	2.9 ±1.0	2.4 ±0.5	1.164	0.330
KL-6 (U/mL)	653 (349, 1223)	919 (416, 1400)	899 (353, 1434)	885 (708, 1203)	685 (249, 1046)	4.288	0.368
ferritin (ng/mL)	625.4 (192.3, 1073.0)	877.0 (93.1, 983.1)	503.0 (195.3, 680.0)	587.0 (253.2, 927.7)	789 (543, 789)	1.809	0.771
CD4/8	1.6 (1.2, 2,7)	1.2 (1.0, 3.2)	2.3 (1.7, 2.6)	1.4 (1.1, 1.9)	2.3 (1.3, 3.0)	6.334	0.176

CK = creatine kinase, LDH = lactate dehydrogenase, TC = total cholesterol, TG = triglyceride, HDL = high-density lipoprotein, LDL = low-density lipoprotein, KL-6 = krebs von den lungen-6.

Note: Qualitative variables were presented as counts (n) and percentages (%) by chi-square test or Fisher's Exact test. Quantitative variables were presented as median (P25, P75) by Kruskal-Wallis test or mean ± SD by one-way ANOVA.

PFTs

80 patients did the PFTs in our study (Table 3). FEV1/FVC in myasthenia group was significantly higher than that in respiratory symptom group (88.2 (81.8, 93.9) *vs* 81.4 (80.1, 83.7), $P < 0.05$). MMEF75/25 in respiratory symptom group was significantly lower than that in myasthenia group and arthritis group (45.3 (34.5, 54.0) *vs* 74.2 (57.2, 99.5), $P < 0.05$). FVC in respiratory symptom group was significantly lower than that in rash group, arthritis group and atypical group (67.2 ± 15.8 *vs* 82.9 ± 17.6, 67.2 ± 15.8 *vs* 78.4 ± 15.6, 67.2 ± 15.8 *vs* 86.8 ± 11.6, $P < 0.05$), and DLCO in respiratory symptom group was also significantly lower than that in rash group, arthritis group and atypical group (44.6 ± 12.3 *vs* 62.8 ± 16.8, 44.6 ± 12.3 *vs* 57.9 ± 13.0, 44.6 ± 12.3 *vs* 67.0 ± 15.5, $P < 0.05$).

Table 3. PFTs in different subgroups of DM

Factors	Rash	Myasthenia	Arthritis	Respiratory	Atypical	Test statistic	*P*
FEV1/FVC	81.0ab (77.5, 86.3)	88.2a (81.8, 93.9)	84.4ab (79.1, 87.7)	81.4b (80.1, 83.7)	82.6ab (67.9, 85.4)	10.336	0.035
MMEF75/25	59.1ab (46.5, 70.5)	74.2a (57.2, 99.5)	76.0a (48.5, 87.5)	45.3b (34.5, 54.0)	65.6ab (31.7, 113.6)	18.234	0.001
FVC	82.9 ±17.6a	78.4 ± 15.6ab	85.7 ± 18.4a	67.2 ± 15.8b	86.8 ± 11.6a	4.085	0.005
DLCO	62.8 ±16.8a	53.7 ±15.2ab	57.9 ± 13.0a	44.6 ± 12.3b	67.0 ± 15.5a	5.560	0.001

FEV1/FVC = forced expiratory volume in 1s/Forced vital capacity, MMEF75/25 = percentage of maximum mid-expiratory flow to estimated value, FVC =percentage of forced vital capacity to estimated value, DLCO = percentage of diffusion capacity for carbon to estimated value.

Note: Quantitative Variables were presented as median (P25, P75) By Kruskal-Wallis test or mean ± SD by one- way ANOVA. Values with letters a, b and significantly different across columns with Bonferroni's comparison tests (P < 0.05).

Myositis antibodies

The differences in myositis antibodies among subgroups included anti-TIF1γ and anti-RO52 antibodies (Table 4). The positive rate of anti-TIF1γ antibodies in rash group was significantly higher than that in arthritis group and respiratory symptom group (29.1% *vs* 0.0%, 29.1% *vs* 0.0%, $P < 0.05$). Atypical group had a higher positive rate of anti-TIF1γ antibodies than arthritis group and respiratory symptom group (27.3% *vs* 0.0%, 27.3% *vs* 0.0%, $P < 0.05$). The positive rate of anti-RO52 antibodies in respiratory symptom group was significantly higher than that in rash group and myasthenia group (83.3% *vs* 49.1%, 83.3% *vs* 30.8%, $P < 0.05$). Arthritis group had a higher positive rate anti-RO52 antibodies than that in rash

group and myasthenia group (85.2% *vs* 49.1%, 85.2% *vs* 30.8%, $P < 0.05$). There were no significant differences in other myositis antibodies ($P > 0.05$).

Table 4. Myositis antibodies in different subgroups of DM

Antibodies	Rash (N = 55) (n/N, %)	Myasthenia (N = 13) (n/N, %)	Arthritis (N = 27) (n/N, %)	Respiratory (N = 30) (n/N, %)	Atypical (N = 11) (n/N, %)	*P*
MDA5	24 (43.6)	7 (53.8)	20 (74.1)	17 (56.7)	4 (36.4)	0.208
TIF1γ	16 (29.1) a	2 (15.4) ab	0 (0.0) b	0 (0.0) b	3 (27.3) a	0.000
Mi-2	4 (7.3)	1 (7.7)	0 (0.0)	1 (3.3)	1 (9.1)	0.646
RO52	27 (49.1) a	4 (30.8) a	23 (85.2) b	25 (83.3) b	6 (54.5) ab	0.000

MDA5 = anti-melanoma differentiation-associated protein 5, TIF1γ = anti-transcription intermediary factor 1-gamma, Mi-2 = anti-chromodomain-helicase-DNA-binding proteins.

Note: Qualitative variables were presented as counts (n) and percentages (%) by chi-square test or Fisher's Exact test. Values with letters a, b and significantly different across columns with Bonferroni's comparison tests ($P < 0.05$).

3.3 Survival analysis

All patients were followed up in our study, and six patients died. The longest follow-up time was 54 months, and the mean follow-up time was 20 months. Kaplan-Meier analysis was used to analyze survival curves among different subgroups (Figure 1). The 1-year and 3-year survival rate of rash groups and atypical symptom groups were 100%. The 1-year and 3-year survival rates of myasthenia groups were both 84.6%. The 1-year and 3-year survival rates of respiratory symptoms groups were both 96.7%. The 1-year and 3-year survival rates of arthritis groups were 96.3% and 88.9%. There were significant differences in cumulative survival rate among the five groups by Log-rank test ($P = 0.048$, $P < 0.05$). The survival rate of rash groups was higher than myasthenia groups ($P = 0.003$, $P < 0.05$) and arthritis groups ($P = 0.018$, $P < 0.05$). There were no significant differences in cumulative survival rate between other groups ($P > 0.05$).

4. Discussion

Our research revealed the characteristics of DM with different initial symptoms. The patients of DM were categorized as rash group, myasthenia group, arthritis group, respiratory symptom group and atypical symptom group according to different initial symptoms. In our study, no significant differences were found in demographics of different subgroups, indicating that age, gender, BMI and smoking had no effect on the first manifestations of DM. The female to male ratio was about 2.7:1 for total patients.

Slightly higher than the 2:1 ratio in previous study [16]. It could have been caused by the regional disparity. 43% (31/72) patients experienced itchy skin during the disease, lower than one American study showed that over 90% of DM patients had pruritus [17] and another American research showed that about 85% of DM patients had itching [18]. The difference might come from the ethnic differences and subjective differences of patients. Studies have confirmed that pruritus in DM is related to IL-31. Lenabasum suppressed the secretion of IL-31, which may be a new therapy for itch in DM [17]. Rash (n=55, 40%) was the most common initial symptoms of DM. DM rash was often associated with itching and photosensitivity. The rashes with pruritus could be distinguished from SLE. The itch degree corresponds to the CDASI (Cutaneous Disease and Activity Severity Index), which can be used to assess the disease activity of patients [17]. About 20% of patients came to the hospital with arthritis as the first symptom. Arthritis in IIM is often characterized by symmetrical, non-aggressive polyarthritis, with the wrists, followed by metacarpophalangeal joints (MCP), interphalangeal joints (PIP) and shoulders [19], similar to rheumatoid arthritis (RA). Clinicians should consider the possibility of IIM when diagnosed seronegative RA. About 22% patients showed respiratory symptom as the first symptom, and ILD was diagnosed after PFTs and chest high-resolution computed tomography (HRCT). Consistent with a previous report that ILD occurred in about 20% - 30% of patients before the diagnosis of myositis [20]. Taking use of high resolution CT (HRCT), the patterns of the myositis associated interstitial pneumonia are divided to the following types: usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), organized pneumonia (OP), acute interstitial pneumonia (AIP), lymphocytic interstitial pneumonia (LIP) [21, 22]. The type of ILD affected the prognosis. OP had a better prognosis than DAD and UIP [20], and myositis associated UIP had a better survival rate than idiopathic pulmonary fibrosis UIP [23]. The incidence of ILD in respiratory symptom groups was higher than rash groups and atypical groups. Respiratory symptom group showed significantly lower levels of FVC and DLCO in PFTs than those in rash group, arthritis group and atypical manifestations group. Restrictive ventilatory impairment is the typical characteristic of ILD, and the decrease of DLCO usually precedes alteration of lung volumes in PFTs. It should be noted that respiratory muscle weakness can also lead to abnormal PFTs. Therefore, PFTs and chest HRCT are both required in those individuals to distinguish the cause. In this study, the difference of TG in subgroups was statistically significant by Kruskal-Wallis tests ($P < 0.05$), but no statistic difference in pairwise comparison with Bonferroni's multiple tests probably because of the relatively small sample size.

Myositis specific antibodies (MSAs) are associated with the diagnosis of myositis, and the clinical manifestations as well as prognosis of myositis [15, 24]. According to the latest classification of DM in ENMC [15], DM-MSAs include anti-melanoma differentiation-associated protein 5 (MDA5), anti-transcription intermediary factor 1-gamma (TIF1γ), anti-nuclear matrix protein 2 (NXP2), anti-small ubiquitin-like modifier activating enzyme (SAE), and anti-chromodomain-helicase-DNA-binding proteins (Mi-2) antibodies. In the present study, we only concentrate on anti-MDA5, anti-TIF1γ and anti-Mi2 antibodies in DM- specific autoantibodies. As only a small number of patients were tested for anti-NXP2 and anti-SAE, these two antibodies were not analyzed. The positive rate of anti-TIF1γ antibodies in the rash group and atypical group was both significantly higher than arthritis group and respiratory symptom

group. Previous researches also indicated that patients with positive anti-TIF1γ antibodies often present typical rash [25]. Additionally, anti-TIF1γ antibodies are highly related to the risk of malignant tumors. The risk of malignance is higher in patients over 39 years of age [26]. Particularly ovarian, lung, pancreatic, stomach, colorectal cancers, and non-Hodgkin's lymphoma are the most common [27]. All 27 patients in arthritis group had negative anti-TIF1γ, and anti-Mi2 antibodies. Similar to a previous study that showed the patients with positive anti-TIF1γ antibodies have lower risk of arthritis [5]. Our data suggested the positive rate of anti-TIF1γ antibodies in arthritis group was significantly lower than rash group and atypical group. Anti-RO52 antibodies is the most common MAAs, and its positive rate in respiratory symptom group and arthritis group was significantly higher than that in rash group and myasthenia group. Anti-RO52 antibodies often co-exists with anti-MDA5 antibodies, and their occurrence correlates with a more severe clinical phenotype and poorer prognosis [28]. The positive rate of MSAs in this study was 70%, which was consistent with the positive rate of over 50% in previous studies of MSAs [29]. Among the 136 patients who received myositis antibodies test, 6 patients (4.4%) had more than one MSAs, higher than 0.2% in a previous study [30], which was inconsistent with the mutual exclusivity of MSA previously studied. It is probably a consequence of the heterogeneity of myositis and the small sample size.

The results of Kaplan-Meier analysis showed that the cumulative survival rates of patients in different initial symptoms were various. In different stages of myositis, non-immune and immune system of cellular and non-cellular mechanisms are the key regulatory steps of inflammation [3, 31]. The different initial symptoms in DM patients may also be related to the different pathological mechanisms. The 3-year survival rate of rash groups was significantly higher than myasthenia groups and arthritis groups in our study. It should be noted anti-TIF1γ antibody is associated with typical rash and higher risk of malignant tumor, and the risk of cancer is related to age [32]. Even though cutaneous features have not been approved associated with cancer, the longer follow-up time is also necessary. Moreover, when patients have vasculopathic lesions (digital pulp ulcers, inverse Gottron’s papules and nailfold capillary abnormalities) or calcium deposition, it should be given more attention and active treatment to avoid refractory myositis [33].

However, this single-center retrospective analysis has several limitations. First, this study was a retrospective study, some missing data leaded to limited indicators of patients included. Second, the sample size is relatively small. Overall, it provided a new way for the classification of DM, and it is necessary to further expand the sample size and carry out more researches in this field.

5. Conclusion

Rash was the most common first symptoms of DM, followed by respiratory symptom, arthritis, myasthenia, and atypical symptom. The positive rate of anti-TIF1γ antibodies in rash group and atypical group was significantly higher than arthritis group and respiratory symptom group. Respiratory symptom group and arthritis group had a significantly higher positive rate of anti-RO52 antibodies than rash group

and myasthenia group. Attention should be paid to PFTs and chest HRCT in patients of respiratory symptom group, which is essential to the early diagnosis of DM-ILD. The 3-year survival rate of rash groups was significantly higher than myasthenia group and arthritis group. Patients need regular follow-up visits to monitor disease changes and improve survival rate.

Declarations

Ethics approval and consent to participate

The research was conducted in accordance with the ethical standards of the Declaration of Helsinki and approved by ethics committee of Zhengzhou University, and obtained informed consent of participants.

Consent for publication

Not applicable.

Competing interests

The authors declared no conflicts of interest.

Availability of data and material

Not applicable.

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Authors' contributions

Yue Sun designed the study and wrote the main manuscript text. Dai-Feng Li and Yin-Li Zhang provided substantial contributions to the design and drafting. Xu Liang provided substantial contributions to the final version, Tian-Fang Li provided overall supervision and the final version.

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Figures

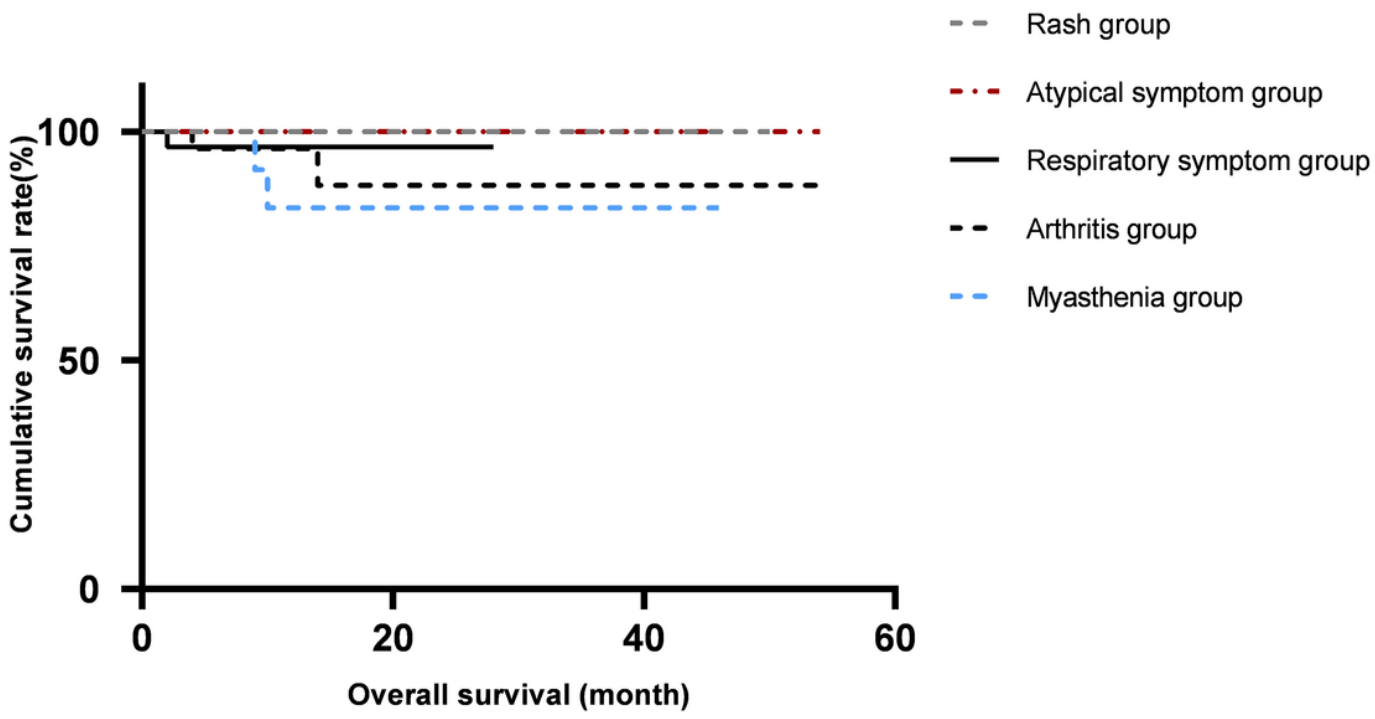

Figure 1

The survival curves of differences subgroups (Kaplan-Meier analysis). There were significant differences among the five groups by Log-rank test (P = 0.048). The 3-year survival rate of rash groups was significantly higher than myasthenia groups (P = 0.003) and arthritis groups (P = 0.018).