Clinical heterogeneities and prognoses of patients with myositis specific antibody negative dermatomyositis: a retrospective study in China

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Abstract

Objective

The clinical features of myositis specific antibody negative dermatomyositis (MSA negative DM) varied greatly, and there were few reports in the literatures. This study aimed to describe and expand the clinical phenotypes and prognoses of MSA negative DM patients.

Methods

MSA negative DM patients were identified from January 2010 to June 2020. We retrospectively reviewed the clinical features and laboratory data. The survival status was followed up until July 31. 2020 SPSS version 21.0 and R version 3.6.1 software were used for the statistical analyses.

Results

A total of 97 MSA negative DM patients were enrolled. The most common type of rashes was heliotrope rash (80.4%). More than half of the patients (55.7%) had interstitial lung disease (ILD), and seven of them developed rapid progressive ILD. There were eleven patients with tumours. During the follow-up, twelve patients died, of whom 5 (41.7%) died due to infection. Two phenotypes of MSA negative DM patients were identified by cluster analysis. Patients in cluster 1 developed muscle weakness, mechanic's hands, arthritis, and ILD more frequently. Patients in cluster 2 had a higher incidence of heliotrope rashes. Patients in cluster 1 tended to have worse prognoses, wherein the 1-year and 5-year survival rates (81.1% and 78.4%, respectively) were lower than those in cluster 2 (97.6% and 95.2%, respectively), with p-value 0.04 and 0.056, respectively.

Conclusion

Through cluster analysis, different clinical phenotypes of MSA negative DM patients were determined. The prognoses of the two subgroups were different in terms of survival rate and cause of death.

Key words

dermatomyositis, myositis specific antibody negative, clinical phenotype, prognoses

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Introduction

Dermatomyositis (DM) is a complex heterogeneous disease characterised by muscle and skin inflammation, along with varying degree of internal organs involvement (1, 2). According to the European Neuro Muscular Center (ENMC) classification criteria, myositis specific autoantibodies (MSAs) play critical roles in the diagnosis of DM (3, 4). Moreover, MSAs can indicate different clinical features and predict prognoses of DM (5-8). For example, DM patients with anti-melanoma differentiation-associated gene 5 (anti-MDA5) antibody usually develop rapid progressive intestinal lung disease (RP-ILD) with poor prognoses, while those with anti-nuclear matrix protein 2 (anti-NXP2) antibody often develop severe muscle weakness and subcutaneous calcifications (9-12).

However, the proportion of patients with MSA negative DM is high. They also demonstrate heterogeneous clinical characteristics and prognoses. We have previously demonstrated that patients with MSA negative DM could develop RP-ILD (13). The current understanding of MSA negative DM, a subtype of DM, is limited. This study aimed to analyse the clinical features and prognoses of patients with MSA negative DM in order to improve our insight into this type of DM.

Materials and methods

Study population

From January 2010 to June 2020, a total of 1016 patients who were clinically suspected DM (these patients had at least one of the classic clinical characteristics: rashes and muscle weakness) underwent the test of MSA at the Department of Rheumatology in China-Japan Friendship Hospital, Beijing, China. The clinical data of the patients were carefully reviewed, and 113 adults were diagnosed with MSA negative DM according to the 2018 ENMC proposed criteria (4). Sixteen patients were diagnosed with overlap syndrome (seven with DM and Sjögren's syndrome, three with DM and systemic sclerosis, two with DM and rheumatoid arthritis, two with DM and psoriasis, one with DM and systemic lupus erythematosus, and one with DM and ankylosing spondylitis). Finally, 97 adult MSA negative DM patients were enrolled in this study. The study protocol was approved by the Ethics Committee of the China-Japan Friendship Hospital (approval number: 2016-117).

Clinical data

The demographics, clinical features and laboratory data of the patients were gathered through detailed records at their first time to our department.

The clinical manifestations included myalgia, proximal limb muscle weakness, cutaneous involvement, Raynaud's phenomenon, dysphagia, arthritis, and interstitial lung disease (ILD). The cutaneous features observed in the patients included heliotrope rash, V sign, shawl sign, mechanic's hands, Gottron's papules and sign, cutaneous ulcer, periungual erythema and subcutaneous calcification.

Cancer-associated myositis was defined as cancer that occurred within 3 years of the disease onset (before or after) (14). The survival status of the patients was followed up until July 31, 2020.

Laboratory data

The laboratory data consisted of routine blood test results, lymphocyte subsets, the levels of serum transaminase (ALT and AST), creatine kinase (CK), lactate dehydrogenase (LDH), albumin (Alb), pre-albumin (Pre-Alb), immunoglobulins (IgG, IgA, and IgM), C-reactive protein (CRP), serum ferritin and anti-nuclear antibody (ANA) spectrum.

Detection of MSA

MSAs (anti-Mi-2, anti-TIF1-γ, anti-MDA5, anti-NXP2, anti-SAE1, anti-SRP, anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ, and anti-OJ) were detected by Immuno Blot (order No. DL 1530-1601-4G; EUROIMMUN, Germany), and the anti-HMGCR autoantibody was detected by ELISA according to the manufacturer's instructions (catalog number:704760, Inova Diagnostics, Inc., USA), both of which have been widely used in clinical practice in China.

ILD evaluation

ILD was diagnosed via high-resolution computer tomography (HRCT) of the

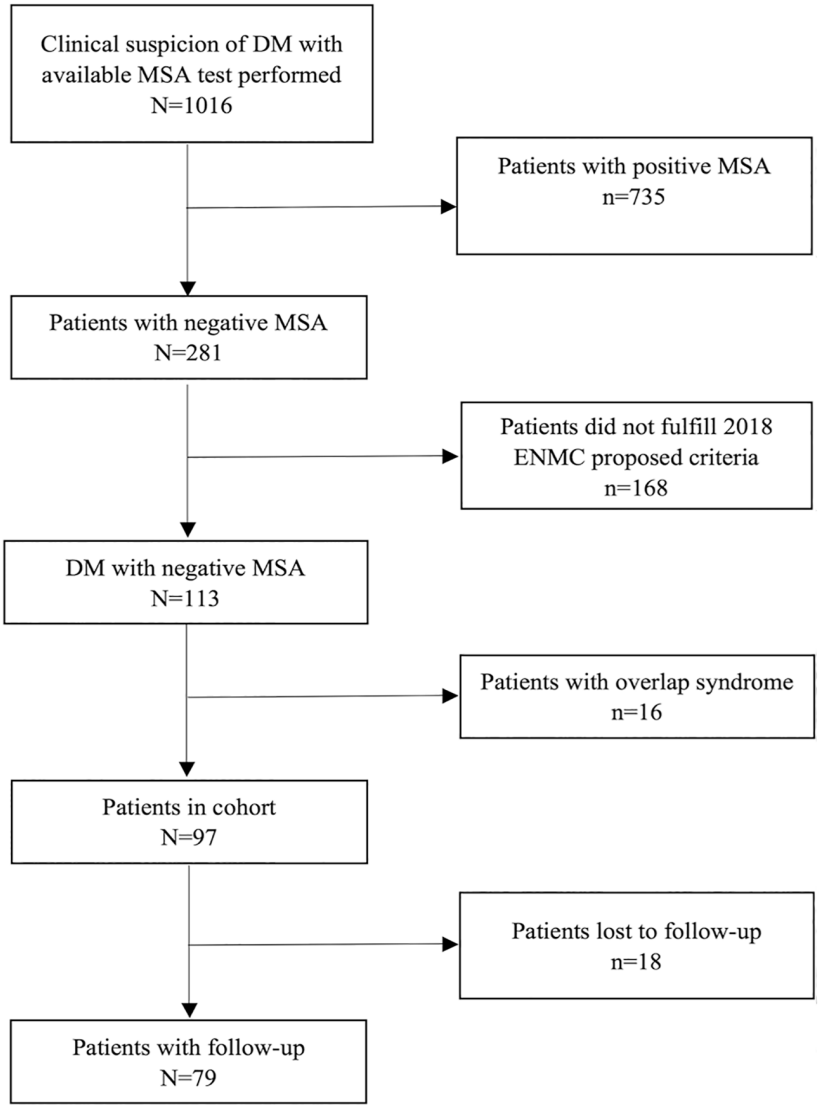

Fig. 1. Flowchart of the study.
MSA: myositis specific autoantibody; ENMC: European Neuro Muscular Centre; DM: dermatomyositis.

chest. A subset of patients with RP-ILD presented with progressive dyspnoea and a worsening of the interstitial changes on HRCT within 1 month from the onset of the respiratory symptoms (15). The classification of ILD, which included usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP) and organising pneumonia (OP) were made via HRCT by two experienced radiologists who were blinded to the clinical features of the patients.

Statistical analysis

SPSS version 21.0 was used for the statistical analyses. The Kolmogorov-Smirnov test was used to evaluate the distribution of each continuous parameter. Statistical differences between groups were calculated using Student's t test (normal distribution), Mann-Whitney U test (non-normal distribution) or the Chi square test. Data were expressed as means ± standard deviation (SD) or median (range P25, P75). Hierarchical cluster analysis was used for classification, and multiple correspondence analysis was used for confirmation by R version 3.6.1 software (10). Classification and regression trees was analysed to find predictor variables using the R software. For the survival analysis, Kaplan-Meier curves were performed on different clusters. All statistical tests were two-sided, and *p*-values of less than 0.05 were considered to be significant.

Results

Overall clinical characteristics and prognoses of MSA negative DM patients

We screened 113 MSA negative DM patients from clinically suspected DM in our cohort. Of the 113 patients, 16 (14.2%) presented with overlap syndrome, which were excluded from the study (Fig. 1). The remaining patients with isolated MSA negative DM (n=97) included 61 females (62.9%) and 36 males (37.1%) (Table I). The average ages of disease onset were 45.26±13.98 years (range from 19 to 81 years), and the durations of DM ranged from 1 to 168 months (median 6 (3-23) months). All patients in this study had cutaneous involvement. Seventy-eight (80.4%) patients presented with heliotrope rashes, 61 (62.9%) patients had Gottron's papules, and 59 (60.8%) patients developed with Gottron's sign. In addition, 86 (88.7%) patients had proximal limb muscle weakness, and 92 (94.8%) patients presented with elevated levels

Table I. The general clinical features of patients with MSA negative DM.

Clinical features	N=97
Age of onset (y)	45.26 ± 13.98
Female/male n (%)	61 (62.9)
Duration (m)	6 (3,23)
Rash types n (%)	97 (100)
Heliotrope rash n (%)	78 (80.4)
V sign n (%)	56 (57.7)
Shawl sign n (%)	42 (43.3)
Mechanic's hands n (%)	31 (32.0)
Gottron's papules n (%)	61 (62.9)
Gottron's sign n (%)	59 (60.8)
Cutaneous ulcer n (%)	9 (9.3)
Periungual erythema n (%)	8 (8.2)
Subcutaneous calcification n (%)	1 (1.0)
Clinical manifestations	
Reynold phenomenon n (%)	6 (6.2)
Myalgia n (%)	54 (55.7)
Muscle weakness n (%)	86 (88.7)
Dysphagia n (%)	21 (21.6)
Arthritis n (%)	35 (36.1)
Interstitial lung disease (ILD) n (%)	54 (55.7)
Rapid progressive ILD n (%)	7 (7.2)
Cancer n (%)	11 (11.3)
Cancer-associated myositis n (%)	10 (10.3)
Laboratory results	
Elevated muscle enzymes n (%)	92 (94.8)
MSA tested at disease onset n (%)	62 (63.9)
MAA positive n (%)	49 (50.5)

MAA: myositis associated antibody.
MAA included ANA, Ro52, CCP, dsDNA, M2, PM-Scl and anti-phospholipid antibody.

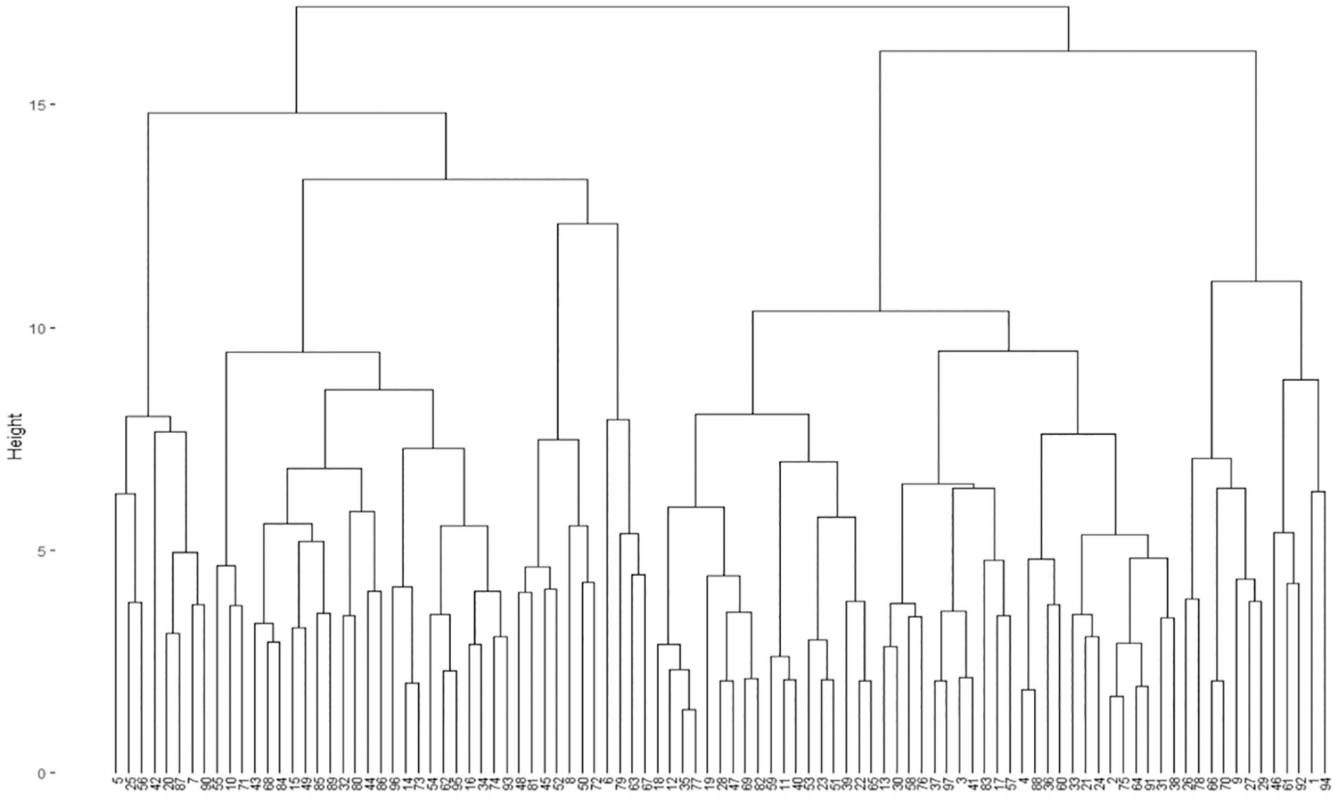

Fig. 2. The cluster analysis of MSA negative DM.
Dendrogram generated using euclidean distance and the Ward agglomerative method. The bold vertical line indicates the height of fusion into clusters p roposed and the x-axis indicates the individuals (n=97) at the bottom of the dendrogram.

of muscle enzymes during disease progression. Considering ten patients with either proximal limb muscle weakness or increased muscle enzymes and one patient with neither proximal limb muscle weakness nor increased muscle enzymes, muscle pathology had done and shown definitive DM for them. Two patients, who presented with typical rashes, were clearly diagnosed as DM with definite interface dermatitis.

More than half of the patients (55.7%) had ILD. In addition, seven patients developed RP-ILD. NSIP (34/54, 63.0%) was the most common pattern observed in the HRCT. Thirty-five (36.1%) patients had arthritis. Twenty-one patients (21.6%) experienced dysphagia.

All patients received glucocorticoid (GC) therapy, of whom 78 patients received immunosuppressant. Cyclophosphamide (CYC) was the most commonly used immunosuppressant (25.6%), followed by calcineurin inhibitors (Cyclosporine A or Tacrolimus, 23.1%) and methotrexate (MTX, 16.7%). Furthermore, seven patients received a combination of two immunosuppressants.

The survival status of the patients was followed up until July 31, 2020. Due to invalid contact information, 18 patients could not be followed up. Twelve of 79 patients died of infection (n=5), cancers (n=4), and other reasons(n=3). The survival time of the patients were from 3 to 67 months. In addition, eleven cases developed tumours (2 with thyroid cancer, 2 with breast cancer, 2 with lung cancer, 1 with cervical carcinoma, 1 with oesophageal cancer, 1 with nasopharyngeal carcinoma, 1 with malignant invasive hydatidiform mole and 1 with lymphoma), of whom 10 cases had cancer-associated myositis.

Clinical subgroups of MSA negative DM patients based on cluster analysis

The MSA negative DM patients were stratified into two clusters by hierarchical cluster analysis (Fig. 2). Multiple correspondence analysis further confirmed the existence of two phenotypes of MSA negative DM patients (Fig. 3). The first cluster included 43 patients (44.3%), and the second cluster included 54 patients (55.7%). Comparisons of the clinical features and laboratory data between two clusters were shown in Table II.

The age of disease onset in cluster 1 (48.72±14.62 years) were older than those in cluster 2 (42.50±12.92 years, p=0.029). All of patients in cluster 1 displayed proximal limb muscle weakness, which had a higher frequency than cluster 2 (100% *vs*. 79.6%). Increased frequencies of mechanic's hands (48.8% *vs*. 18.5%), Gottron's sign (83.7% *vs*. 42.6%) and Gottron's papules (76.7% *vs*. 51.9%) were observed in the cluster 1 patients, while heliotrope rash (65.1% *vs*. 92.6%) was more common in cluster 2 patients (Table II). None of the patients in cluster 2 had cutaneous ulcer, periungual erythema or subcutaneous calcification, and the frequencies of the first two types of rashes in cluster 1 were significantly higher(p<0.05). The incidences of extra-muscular clinical features, such as dysphagia (34.9% *vs*. 11.1%), arthritis (62.8% *vs*. 14.8%) and ILD (86.0% *vs*. 31.5%), were also significantly higher in cluster 1 than those in cluster 2. The incidences of tumours

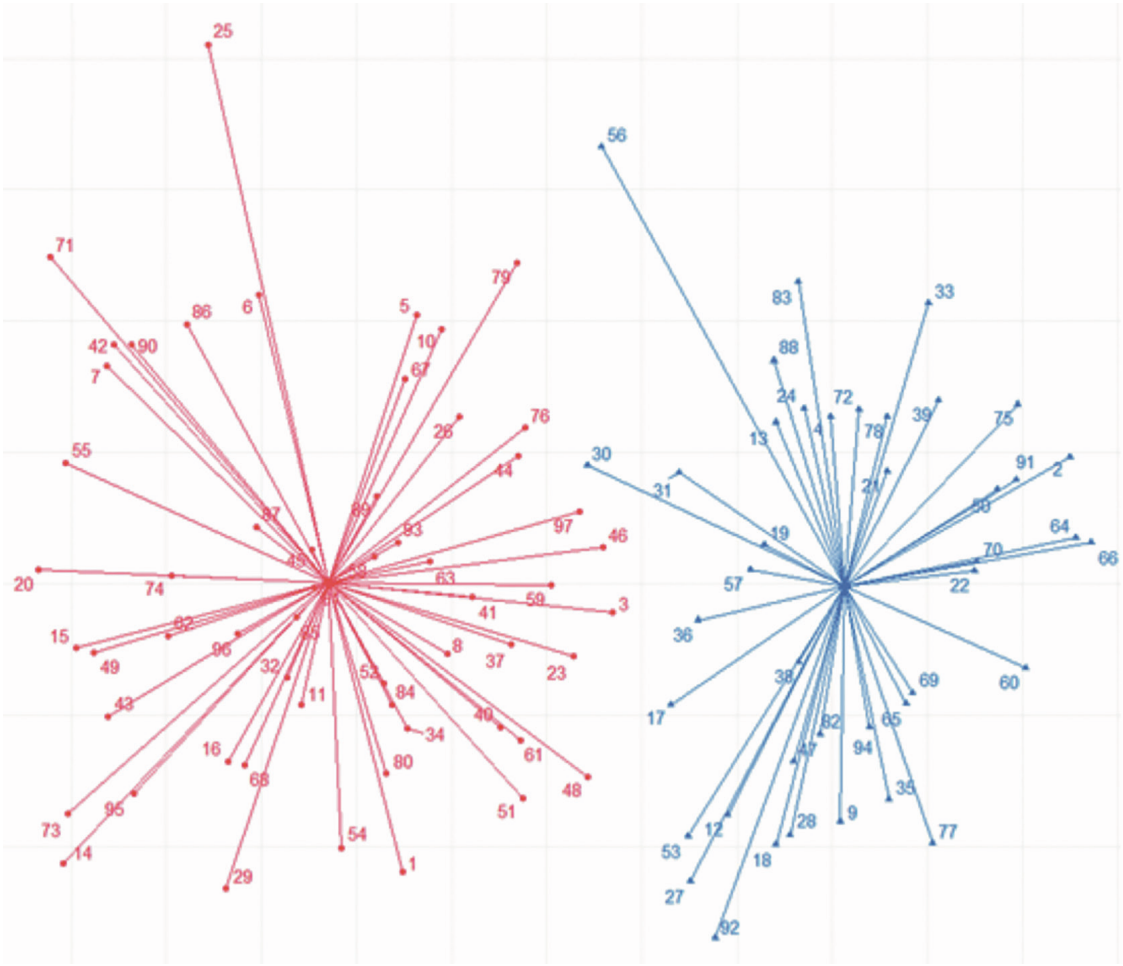

Fig. 3. The confirmation of two clusters by multiple correspondence analysis.
Factor map showing the raw data (individuals) used to generate the dendrogram. On the factorial map, the colors indicate individuals according to the cluster to which they belong, while the lines indicate how far individuals from the centre.

were comparable in the two clusters (14.0% *vs*. 9.3%).
Patients in cluster 2 showed higher levels of Alb than those in cluster 1 with statistical significance. However, patients in cluster 1 showed a tendency of higher levels of CRP and ferritin than those in cluster 2, which was not significant. Other laboratory data, including blood routine test and spectrum of muscle enzymes, were comparable between the two clusters.

The predictor of stratification into two subgroups in MSA negative DM patients

Significant differences in clinical features were observed between cluster 1 and cluster 2. Therefore, it was necessary to find predictors in MSA negative DM patients in order to classify them into different subgroups. The clinical data of 97 MSA negative DM patients were analysed. The variables included in the unsupervised analysis were gender, age of disease onset (in the form of continuous variables), myalgia, proximal limb muscle weakness, elevated muscle enzymes, heliotrope rash, V sign, shawl sign, mechanic's hands, Gottron's papules and sign, cutaneous ulcer, periungual erythema, Raynaud phenomenon, dysphagia, arthritis, ILD and cancer by regression tree model. Three variables were found to affect the results: ILD, arthritis, and V sign. They were predictors of stratification for the patients into different clusters with a total accuracy of 83.51% (Fig. 4). The accuracies of the different clusters were 84.62% and 82.76%, respectively. MSA negative DM patients with ILD and arthritis belonged to cluster 1. If they developed ILD but neither with arthritis nor typical V sign, they can also be in the cluster 1. If the MSA negative DM patients did not complicate with ILD, they belonged to cluster 2, but it should be noted that some patients with ILD and typical V sign while no arthritis, they also belonged to cluster 2. Therefore, it highlights the involvement of other systems except muscle and skin in cluster 1, while the tendency of other system involvement decreased in cluster 2.

The prognoses of patients in the two clusters

The prognoses of patients in the two clusters were compared. The follow-up period of the 79 MSA negative DM patients ranged from 1 to 117 months. Eight and four deaths were reported in cluster 1 and 2, respectively. The patients in cluster 1 tended to have worse prognoses, despite a p value of 0.128 in the survival analysis (Fig. 5). The survival time of patients who died in cluster 1 ranged from 3 to 14 months (mean 6.6±3.9 months), while those in cluster 2 ranged from 3 to 67 months (mean 38.0±31.4 months). In addition, the 1-year survival rate in cluster 1 (30/37, 81.1%) was significantly lower than that in cluster 2 (41/42, 97.6%, p=0.04). Moreover, the 2-year and 5-year survival rates in cluster 1 (78.4%) showed

Table II. The clinical phenotypes of two subtypes by cluster analysis.

Clinical features	Cluster 1 (n=43)	Cluster 2 (n=54)	*p*
Age at onset (y)	48.72 ± 14.62	42.50 ± 12.92	0.029*
Female n (%)	27 (62.8)	34 (63.0)	0.986
Duration (m)	4.0 (2.5,18.0)	8.0 (3.8, 24)	0.153
Rash types			
Heliotrope rash, n (%)	28 (65.1)	50 (92.6)	0.001*
V sign, n (%)	21 (48.8)	35 (64.8)	0.114
Shawl sign, n (%)	19 (44.2)	23 (42.6)	0.875
Mechanic's hands, n (%)	21 (48.8)	10 (18.5)	0.001*
Gottron's papules, n (%)	33 (76.7)	28 (51.9)	0.012*
Gottron's sign, n (%)	36 (83.7)	23 (42.6)	<0.001*
Cutaneous ulcer, n (%)	9 (20.9)	0	0.001*
Periungual erythema, n (%)	8 (18.6)	0	0.003*
Subcutaneous calcification, n (%)	1 (2.3)	0	0.443
Clinical manifestations			
Raynaud's phenomenon, n (%)	4 (9.3)	2 (3.7)	0.476
Myalgia, n (%)	24 (55.8)	30 (55.6)	0.980
Muscle weakness, n (%)	43 (100)	43 (79.6)	0.005*
Elevated muscle enzymes, n (%)	42 (97.7)	50 (92.6)	0.508
Dysphagia, n (%)	15 (34.9)	6 (11.1)	0.005*
Arthritis, n (%)	27 (62.8)	8 (14.8)	<0.001*
Interstitial lung disease (ILD) n (%)	37 (86.0)	17 (31.5)	<0.001*
Rapid progressive ILD, n (%)	5 (11.6)	2 (3.7)	0.270
Cancer, n (%)	6 (14.0)	5 (9.3)	0.688
Death, n (%)	8 (18.6)	4 (7.4)	0.135
Laboratory results			
MAA positive, n (%)	24 (55.8)	25 (46.3)	0.352
WBC (*10^9/l)	7.28 ± 3.78	7.02 ± 3.06	0.710
N (*10^9/l)	5.03 ± 3.68	5.20 ± 3.02	0.804
L (*10^9/l)	1.26 ± 0.69	1.16 ± 0.62	0.483
CD4 (cell/ul)	564 ± 370	569 ± 334	0.942
N/L ratio	3.22 (2.31, 5.58)	3.71 (2.38, 9.74)	0.397
ALT (U/L)	36 (26,92)	31.5 (21, 53)	0.057
AST (U/L)	34 (20, 78)	30 (18, 48)	0.100
LDH (U/L)	283 (205, 402)	296 (193, 339)	0.627
CK (U/L)	71 (33, 314)	77 (36, 225)	0.856
Alb (g/L)	36.14 ± 4.00	38.24 ± 4.85	0.026*
ProAlb (mg/L)	193.14 ± 89.42	211.38 ± 90.27	0.331
IgG (mg/dl)	1152.83 ± 460.93	1166.00 ± 594.29	0.906
IgA (mg/dl)	199.81 ± 85.45	225.80 ± 139.42	0.269
IgM (mg/dl)	102 (68, 135)	108 (70, 149)	0.617
CRP (mg/dl)	0.45 (0.22, 1.39)	0.30 (0.17, 0.85)	0.070
Ferritin (ng/ml)	273.9 (136.1,660.3)	168.2 (63.3,318.2)	0.084

MAA: myositis associated antibody. *$p<0.05$.

a downward trend than those in cluster 2 (95.2%, $p=0.056$).

Infection (50%) was the most common reason of death in cluster 1, followed by tumours (37.5%). The survival time of patients who died of severe infection were less than 6 months in cluster 1. In contrast, only one patient (25%) died of infection in cluster 2. Two deaths were caused by other reasons (50%, such as cerebral infarction) in cluster 2.

Discussion

In this study, we described the clinical characteristics and prognoses of MSA negative DM patients in the largest Chinese cohort for the first time. Two main subtypes of MSA negative DM patients were determined by cluster analysis. Those in cluster 1 mainly presented with myositis, mechanic's hands, ILD, and arthritis. These features were similar to the clinical spectrum of the anti-synthetase syndrome (ASS) (16). Patients in cluster 2 seemed to exhibit less extra-muscular features and had better prognoses.

Patients with MSA negative DM had typical DM rashes and muscle involvement, according to various classification criteria (4, 17). The main subtype of rashes observed in these patients was heliotrope rash, followed by Gottron's papules and Gottron's sign. However, there existed significant different frequencies between clusters. The incidence of Gottron's papules or Gottron's sign was higher, while the incidence of heliotrope rash was lower in cluster 1. In addition, patients in cluster 1 had higher frequencies of myositis, mechanic's hands, ILD, arthritis and other symptoms. Based on the proposed clinical classification criteria for ASS, patients in cluster 1 seemed to be similar with ASS (18, 19). They suffered from the characteristic triad syndrome of myositis, ILD and arthritis, although without the typical autoantibodies that target aminoacyl transfer RNA synthetases. Moreover, the frequency of mechanic's hands was higher, which is also a predominant cutaneous feature of ASS (16). However, the increased proportion of Gottron's papules or Gottron's sign in our study (>70%) was not a significant feature of ASS. According to previous reports, only about 20% patients with ASS had Gottron's papules or Gottron's sign (20, 21). As we know, eight types of autoantibodies targeting aminoacyl transfer RNA synthetases have been identified so far (22). For patients in cluster 1, we only detected the five common autoantibodies targeting aminoacyl transfer RNA synthetases. Therefore, there might be a possibility that patients of cluster 1 were actually ASS, but our current detection method cannot cover the other three rarer types of autoantibodies. In addition, there may be new autoantibodies existed in this cluster, especially autoantibodies targeting aminoacyl transfer RNA synthetases. Further researches are needed to examine this phenomenon and explore new autoantibodies in future.

Patients in cluster 2 had lower incidences of systemic involvement and better prognoses than those in cluster 1. The incidence of internal organs involvement, such as ILD and dysphagia, was lower. The majority of patients had good prognoses. Furthermore, higher levels of Alb and lower levels of ferritin were observed, which might be related to the low disease activity in these patients. Previous studies have reported that reduced levels of Alb existed in the majority of the anti-NXP2 positive DM patients, who mainly

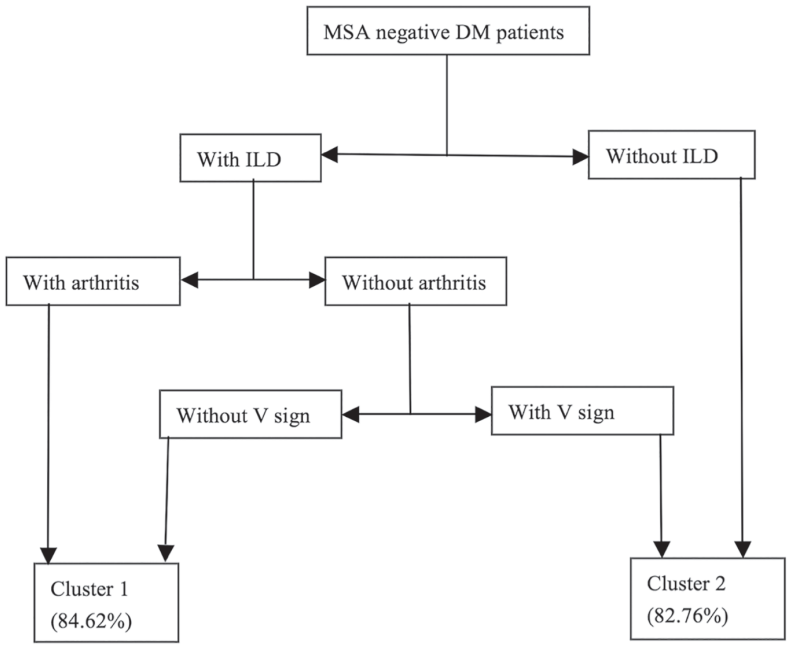

Fig. 4. The predictors of clinical features to position patients to different clusters by classification and regression trees.

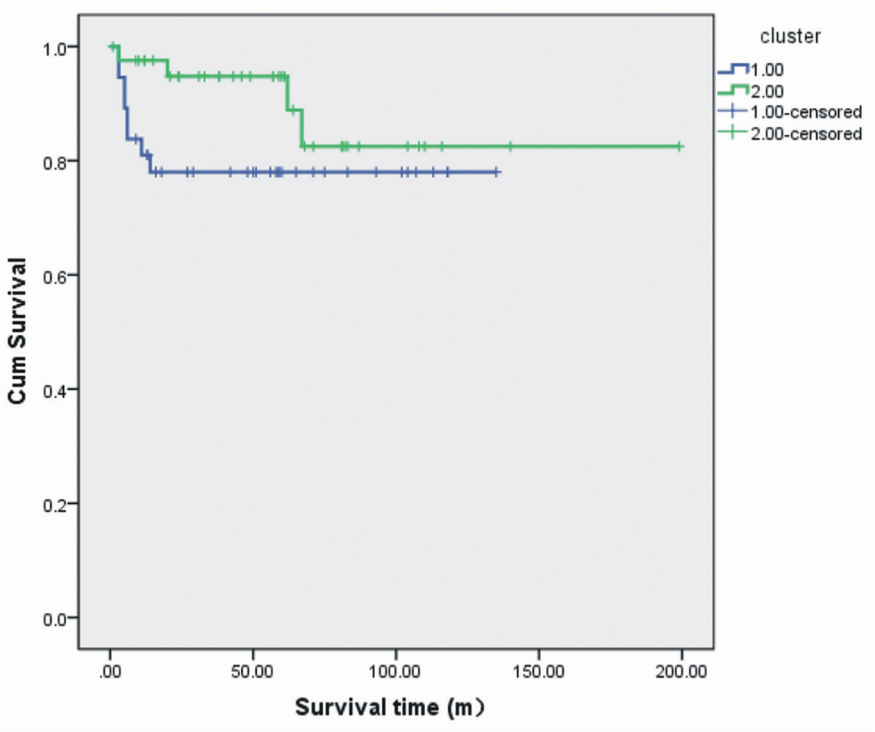

Fig. 5. The survival curve between cluster 1 and cluster 2.

presented with severe muscle weakness (23). Meanwhile, high ferritin expression was associated with poor prognosis in anti-MDA5 positive DM patients (24). In summary, these finding indicated that patients in cluster 2 might have mild disease activity and good prognoses.

The main cause of death in this study was infection, especially severe pneumonia. Five patients died of infection within 6 months. This finding was consistent with previous literatures (25). ILD, especially RP-ILD, is the most common and severe complication in DM, leading to the increase mortality (2, 26, 27). However, it should be noted that no patient in our cohort died of RP-ILD, which meant that RP-ILD in MSA negative DM had a better response to GC and immunosuppressant. There were 11 patients with cancers, including solid tumours and haematological tumours. In terms of the incidence of cancer, it was lower than the majority DM patients (about 20%) (28, 29). Nevertheless, it is still very important to routinely screen cancers during follow-up in MSA negative DM patients.

Significant differences in prognoses were observed between the two clusters. Patients in cluster 1 demonstrated worse prognoses in terms of survival time and survival rate than those in cluster 2. The 5-year survival rate in cluster 1 was about 80%, while the 5-year survival rate in cluster 2 showed better with over 95%. This result was similar to a recent research report (30). The difference may be related to the following two aspects. The first one was that the patients in cluster 1 had high disease activity, who had more organs involvement, including ILD. The second reason was the different causes of death. Patients in cluster 1 died mainly from early severe infection.

These characteristics above indicated that MSA negative DM was a unique subtype of DM in clinical features and prognoses. It was extremely critical to find early predictors to stratify them into different clusters. Our study found that there were three clinical characteristics in clinical practice, ILD, arthritis and V Sign, which could play key roles in early classification of MSA negative DM. This result might be related to the features of ASS, in which ILD and arthritis were both items in classification criteria (18, 19).

Our research also had some limitations. First, this was a cross-sectional retrospective study. Clinical symptoms were collected from the original medical records. Second, according to the previously reported MSA positive rate of 60–80%, there should have been more patients with MSA negative DM in our centre (31, 32). However, the sample size of MSA negative DM was reduced based on the 2018 ENMC proposed classification criteria. A major reason

was that some patients did not have the typical rashes observed in DM. Third, the time span for this study was relatively large (over 10 years). Some patients lost follow-up, which might affect the analysis of prognoses. The last limitation was that some MSA negative DM patients had myositis associated antibodies (MAAs). DM patients with MAAs sometimes also show certain phenotype (33). While, we just focused on MSAs not MAAs on DM patients. Therefore, it is necessary to set strict standards in future studies.

Conclusion

MSA negative DM is a unique subtype of DM with high heterogeneity. Two subtypes of MSA negative DM patients were identified by cluster analyse. Patients in one cluster resembled ASS and had worse prognoses.

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