Phenotypic Clusters and Survival Analyses in Interstitial Pneumonia with Myositis-Specific Autoantibodies

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Abstract

Background: Interstitial pneumonia (IP) is one of the common pulmonary complications of idiopathic inflammatory myopathy (IIM), among which myositis-specific autoantibodies (MSA) are specific for IIM diagnosis and prognosis. However, IP patients with MSA (MSA-IP) have not been well described. The study aimed to explore the phenotypic clusters and prognosis of MSA-IP patients.

Methods: A total of 124 MSA-IP patients were prospectively enrolled for analysis. Serum MSA were detected using immunoprecipitation. Radiographic patterns of IP were determined according to the classification of idiopathic IPs. The clusters of MSA-IP patients were identified using cluster analysis. Potential risk factors of acute onset and short-term prognosis were also analyzed.

Results: There were four clusters of MSA-IP patients. Cluster 1 patients were elders with chronic onset and usual interstitial pneumonia pattern on CT scan. Cluster 2 patients were all positive for anti-aminoacyl-tRNA antibodies, predominantly females and had frequent respiratory symptoms. Patients of cluster 3 showed multi-system involvements with nonspecific interstitial pneumonia pattern. Patients of cluster 4 had severe respiratory symptoms with anti-MDA5. The patients of cluster 3 (OR 6.682, 95% CI 1.560–28.622, *P*=0.011) or cluster 4 (OR 6.057, 95% CI 1.715–21.388, *P*=0.005) were susceptible to acute onset. The patients of cluster 4 were prone to disease progression (HR 2.711, 95% CI 1.128–6.519, *P*=0.034), which was consistent with the Kaplan–Meier curves.

Conclusions: Four distinctive clusters were determined by cluster analysis suggesting the characteristics, serological antibodies and prognosis of MSA-IP.

Background

Interstitial lung diseases (ILDs) are a heterogeneous group of diffuse and fibrotic pulmonary disorders with extensive morbidity and mortality, characterized by the loss of alveolar-capillary functional structures [1]. ILDs are generally classified into four subgroups, including known-causes diseases such as occupational and environmental exposure, connective tissue diseases (CTDs) and drug-related ILDs; idiopathic interstitial pneumonias (IIPs); granulomatous lung disorders such as sarcoidosis; and specific entities [2]. The underlying causes of some ILDs are still unknown, leading to challenges of early diagnosis and treatment [1, 3].

Interstitial pneumonia (IP) is a well-acknowledged manifestation of CTD. IP occurring within the context of CTD is referred to as CTD-associated IP (CTD-IP) [4, 5]. Approximately 15% of ILD patients were diagnosed as CTD-ILD after evaluation [6]. IP can be the primary or sole manifestation of CTD [7], leading to difficulties in accurate diagnosis at the first clinical visit. When IP patients are excluded of known causes and do not satisfy diagnostic criteria for any CTD, combined with clinical, serologic, and/or morphologic features that probably stem from underlying autoimmune conditions, they are diagnosed as IP with autoimmune features (IPAF) [5].

Idiopathic inflammatory myopathies (IIMs) are one of the unusual subtypes of CTDs. IIMs are characterized by skeletal muscle inflammation, and contain polymyositis (PM), dermatomyositis (DM), amyopathic dermatomyositis (ADM), inclusion body myositis etc. [8, 9]. IP is one of the most common extra-muscular manifestations of IIM. [10] The prevalence of IIM-associated ILD is reported to range from 19.9–86% [11–17]. The autoantibodies of IIM consist of myositis-specific autoantibodies (MSA) and myositis-associated autoantibodies (MAA). MSA are highly specific and include anti-aminoacyl-tRNA-synthetase antibodies (anti-ARS), anti-Mi-2, anti-MDA5 and so on, whereas MAA are less specific and can be detected in other CTDs [11–17]. MSA are essential for indicating clinical characteristics, diagnosis and prognosis of IIM [19].

Previous studies have mainly focused on PM/DM secondary ILDs [20]. However, clinical characteristics and prognosis of IP with positive MSA (MSA-IP), irrespective of whether IIM has been diagnosed, are vague. Cluster analysis is an effective method for identifying homogeneous phenotypes among patients with heterogeneous disorders [21, 22]. Therefore, this study aimed to explore clinical characteristics, potential risk factors for acute onset and progression of MSA-IP patients using cluster analysis.

Methods

Study cohort

A total of 2,115 patients with IP from Beijing Chao-Yang Hospital were sequentially included from January 2017 to September 2019 prospectively. IP was diagnosed according to the American Thoracic Society (ATS) and European Respiratory Society (ERS) Consensus Classification of IIPs [23]. All patients with IP underwent clinical examinations, laboratory tests, chest high-resolution computed tomography (HRCT), pulmonary function tests, and if necessary, pathological examinations at their first clinical visits [23].

Among enrolled patients, 30 patients were diagnosed with PM, 20 with DM, 33 with ADM and 41 with IPAF, according to the European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) classification criteria for IIM [24] and the ERS/ATS research statement of IPAF [5]. Of the 2,115 patients with IP, 42 underwent pathological examinations of lungs.

Data collection and definitions

At the first clinical visit, the patient medical records were reviewed to uniformly extract clinical data including demographics (age, sex, and smoking status), patient-reported information (date of symptom onset), clinical manifestations, physical examinations and comorbidities.

Serological markers were obtained within one month of presentation to the clinic including C-reactive protein, erythrocyte sedimentation rate, fibrinogen, immunoglobulin (Ig) A, IgG and IgM. Levels of autoantibodies, creatine kinase and cardiac troponin I were also recorded. MSA, including anti-ARS (anti-

Jo-1, anti-PL-7, anti-PL-12, anti-OJ, and anti-EJ), anti-Mi-2, anti-MDA5, anti-TIF1γ, anti-NXP2, and anti-SAE were detected by immunoprecipitation as previously reported [25–27].

All enrolled patients underwent chest HRCT with a 1-s scan time, 0.625-mm sections, and 10-mm intervals from the lung apex to the base including both lungs in the field of view. Each HRCT scan was reviewed independently by two experienced thoracic radiologists blinded to the clinical data. HRCT patterns were assessed according to the classification of IIPs for the presence of usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), organic pneumonia, or acute interstitial pneumonia (AIP) patterns [23]. The interobserver correlation was good. The kappa value was 0.83.

Pulmonary function test was performed for each patient. The test items included forced vital capacity (FVC), and the diffusing capacity of the lung for carbon monoxide (DLCO) using the single-breath method [28].

The smoking status was categorized into non-smokers, ex-smokers (quit smoking ≥ 12 months previously) and current smokers (currently smoking or quit smoking < 12 months previously). Acute (or subacute) onset was defined as less than three months from symptoms onset to the first clinical visit, and chronic onset was defined as more than three months. Malignancy was recorded if it occurred within three years before or after a positive detection of MSA [29]. Pulmonary hypertension was considered if the tricuspid regurgitation velocity ≤ 2.8 m/s and/or the systolic pulmonary arterial pressure ≥ 37 mmHg in echocardiography [30].

Follow-up and endpoint of the study

The outcome of this study was the progression of IP defined as a relative decrease of FVC% predicted ≥ 10%, a relative decrease of DLCO% predicted ≥ 15%, or death within 6 months of diagnosis [31]. The follow-up interval was 3 or 6 months and the follow-up period ended in September 2019. Survival time was calculated from the onset of symptoms to the outcome or end of the follow-up period.

Statistical analysis

Quantitative data were reported as means ± standard deviations or medians (interquartile ranges), and qualitative data were reported as numbers and percentages. Variables involved in cluster analysis included a binary had or did not have pulmonary symptoms (including cough, dyspnea), a binary had or did not have skeletal muscle symptoms (including proximal muscle weakness, dysphagia), a binary had or did not have UIP pattern, and the subtypes of MSA (anti-ARS or subtypes of anti-non-ARS MSA). These variables were available for all participants. Analysis of variance was used for comparisons of normally distributed quantitative data, the non-parametric Mann–Whitney U test was used to compare quantitative data with a non-normal distribution, and the chi-square test was used for comparisons of qualitative data. Multivariable Logistic regression was applied in determining potential risk factors for acute onset. Survival curves were obtained using Kaplan–Meier curves and compared with log-rank tests. The multivariable Cox proportional hazards model was constructed to identify prognostic factors. Statistical

analysis was performed using SPSS software (version 23.0, IBM), and $P < 0.05$ was statistically significant.

Results

Demographics

The patients with MSA-IP were categorized into four clusters based on clinical manifestations, myositis autoantibodies and HRCT patterns using cluster analysis (Fig. 1). A total of 124 patients with MSA-IP were enrolled in cluster analysis after evaluation (Additional file 1: Figure S1). As shown in Additional file 2: Table S1, the mean age of study population was (57.5 ± 11.2) years, and 58.1% were females. Chronic onset (57.3%) was common. Cluster 1 had 25 (20.2%) patients with mean age of (60.8 ± 12.3) years, and 80% had chronic onset. Cluster 2 was the largest cluster (54/124, 43.6%) with the highest proportion of females (74.1%, $P = 0.008$). Cluster 3 comprised 15 patients and acute onset was common (60.0%, $P = 0.023$). Cluster 4 had the smallest proportion of females (36.7%, $P = 0.008$) and a high proportion of patients with acute onset (56.7%).

Clinical characteristics

In the study population, pulmonary involvement was the most common (Table 1). Cough and dyspnea were frequently observed in cluster 1 (88%, 68%) and cluster 2 (88.9%, 88.9%). In cluster 3, proximal muscle weakness (66.7%, $P < 0.001$), morning stiffness (26.7%, $P = 0.036$), joints swelling (40%, $P = 0.001$) and cutaneous involvement were present (Table 1 and Additional file 3: Table S2). Patients in cluster 4 were characterized by fever (56.7%, $P = 0.033$) and cough (93.3%, $P < 0.001$).

Table 1
Clinical characteristics of four clusters

	All	Cluster 1	Cluster 2	Cluster 3	Cluster 4	X^2	*P* value*
Fever, n (%)	46 (37.1%)	5 (20.0%)	20 (37.0%)	4 (26.7%)	17 (56.7%)	8.755	0.033
Proximal muscle weakness, n (%)	10 (8.1%)	0	0	10 (66.7%)	0	43.232	< 0.001
Dysphagia, n (%)	4 (3.2%)	1 (4.0%)	1 (1.9%)	2 (13.3%)	0	6.283	0.099
Cough, n (%)	103 (83.1%)	22 (88.0%)	48 (88.9%)	6 (40.0%)	28 (93.3%)	22.194	< 0.001
Dyspnea, n (%)	95 (76.6%)	17 (68.0%)	48 (88.9%)	6 (40.0%)	24 (80.0%)	15.546	0.001
Arthralgia, n (%)	32 (25.8%)	3 (12.0%)	14 (25.9%)	7 (46.7%)	8 (26.7%)	5.750	0.125
Morning stiffness, n (%)	11 (8.9%)	0	4 (7.4%)	4 (26.7%)	3 (10.0%)	7.279	0.036
Joints swelling, n (%)	11 (8.9%)	1 (4%)	`4 (7.4%)	6 (40%)	0	14.861	0.001
Progression, n (%)	53 (42.7%)	11 (44%)	25 (46.3%)	4 (26.7%)	13 (43.3%)	1.883	0.597
Death, n (%)	3 (2.4%)	1 (4%)	2 (3.7%)	0	0	1.574	0.731

Values were given as n (%).

*, comparisons among four clusters.

MSA and laboratory measurements

Among 124 patients with MSA-IP, 60.5% were positive for anti-ARS, in which anti-Jo-1 and anti-PL-7 were the most frequent subtypes, and anti-MDA5 was the most common subtype of anti-non-ARS MSA (Table 2). All cluster 2 patients were positive for anti-ARS, in which anti-Jo-1 (24.1%, $P = 0.012$) and anti-EJ (31.5%, $P < 0.001$) were representative. The composite physiologic index was the highest in cluster 2 (43.2 ± 12.2, $P = 0.025$). In cluster 3, anti-PL-7 (26.7%, $P = 0.010$) was common and cardiac troponin I was elevated [0.03 (0.02, 0.06) ng/ml, $P = 0.019$] (Table 2). The distinctive MSA subtypes of cluster 4 were anti-MDA5 (36.7%, $P < 0.001$) and anti-Mi-2β (26.7%, $P < 0.001$). Supplementary laboratory tests were shown in Additional file 4: Table S3.

Table 2
MSA and parameters of four clusters

	All	Cluster 1	Cluster 2	Cluster 3	Cluster 4	T/U/X^2	*P* value*
Anti-ARS, n (%)	75 (60.5%)	11 (44.0%)	54 (100%)	10 (66.7%)	0	84.280	< 0.001
Anti-non-ARS MSA, n (%)	49 (39.5%)	14 (56.0%)	0	5 (33.3%)	30 (100%)	84.280	< 0.001
Anti-Jo-1, n (%)	20 (16.1%)	4 (16.0%)	13 (24.1%)	3 (20%)	0	10.293	0.012
Anti-PL-7, n (%)	20 (16.1%)	4 (16.0%)	12 (22.2%)	4 (26.7%)	0	10.441	0.010
Anti-PL-12, n (%)	9 (7.3%)	2 (8.0%)	7 (13.0%)	0	0	5.260	0.110
Anti-OJ, n (%)	7 (5.7%)	1 (4.0%)	5 (9.3%)	1 (6.7%)	0	3.088	0.326
Anti-EJ, n (%)	19 (15.3%)	0	17 (31.5%)	2 (13.3%)	0	19.819	< 0.001
Anti-SRP, n (%)	8 (6.5%)	4 (16.0%)	0	1 (6.7%)	3 (10%)	5.695	0.092
Anti-Mi-2α, n (%)	3 (2.4%)	2 (8.0%)	0	0	1 (3.3%)	2.310	0.421
Anti-Mi-2β, n (%)	10 (8.3%)	2 (8.0%)	0	0	8 (26.7%)	16.133	< 0.001
Anti-TIF1γ, n (%)	8 (6.5%)	3 (12.0%)	0	0	5 (16.7%)	4.211	0.211
Anti-MDA5, n (%)	15 (11.8%)	2 (8.0%)	0	2 (13.3%)	11 (36.7%)	22.219	< 0.001
Anti-NXP2, n (%)	4 (3.2%)	0	0	2 (13.3%)	2 (6.7%)	5.759	0.076
Anti-SAE1, n (%)	1 (0.8%)	1 (4.0%)	0	0	0	1.823	0.671
RF positive, n (%)	13 (10.5%)	0	4 (8.9%)	3 (25.0%)	6 (26.1%)	8.290	0.024

Values were given as n (%), median (interquartile range) or mean (standard deviation).

*, comparisons among four clusters.

Abbreviations: RF, rheumatoid factor; cTNI, cardiac troponin I; CPI, composite physiologic index; OI, oxygenation index; ARS, aminoacyl-tRNA synthetase; MSA, myositis specific antibodies.

	All	Cluster 1	Cluster 2	Cluster 3	Cluster 4	T/U/X^2	*P* value*
cTNI, ng/ml	0 (0, 0.01)	0 (0, 0.01)	0 (0, 0.01)	0.03 (0.02, 0.06)	0.01 (0, 0.01)	9.904	0.019
OI, mmHg	353.7 (311.9, 434.2)	356.0 (337.9, 397.1)	353.7 (296.0, 419.1)	436.8 (325.1, 457.8)	345.6 (279.3, 410.5)	1.867	0.600
CPI	38.9 ± 14.3	34.6 ± 13.9	43.2 ± 12.2	30.5 ± 18.9	40.3 ± 11.4	3.314	0.025
Values were given as n (%), median (interquartile range) or mean (standard deviation).							
*, comparisons among four clusters.							
Abbreviations: RF, rheumatoid factor; cTNI, cardiac troponin I; CPI, composite physiologic index; OI, oxygenation index; ARS, aminoacyl-tRNA synthetase; MSA, myositis specific antibodies.							

HRCT findings

Among 124 patients, the most frequent HRCT pattern was NSIP (34.7%) followed by UIP (20.2%) (Additional file 5: Table S4). Cluster 1 patients all had UIP pattern, and NSIP pattern was frequent in cluster 3 (53.3%, $P < 0.001$). In cluster 4, AIP pattern (23.3%, P 0.001) was representative.

Risk factors for acute onset

Adjusted for age, sex, and smoking status, the patients in cluster 3 (OR 6.682, 95% CI 1.560–28.622, $P = 0.011$) and cluster 4 (OR 6.057, 95% CI 1.715–21.388, $P = 0.005$) were more likely to have acute onset by multivariable Logistic regression analysis (Table 3).

Table 3
Multivariable Logistic regression model for acute onset

	P value	OR	95% CI of OR
Age*	0.127	1.028	0.992–1.066
Female	0.587	1.364	0.446–4.175
Non-smokers#	0.643		
Ex-smokers	0.618	1.406	0.369–5.365
Current smokers	0.648	0.732	0.192–2.795
Cluster&	0.022		
Cluster 2	0.074	2.883	0.903–9.204
Cluster 3	0.011	6.682	1.560-28.622
Cluster 4	0.005	6.057	1.715–21.388

*, age at the diagnosis; #, take non-smokers as a reference; &, take cluster1 as a reference.

Abbreviations: OR, odds ratio

Survival

The Kaplan–Meier curves showed that the prognosis of cluster 4 was the worst among all other clusters (χ^2 = 9.138, log rank *P* = 0.028) (Fig. 2). The median survival time of cluster 4 was also the shortest (Additional file 6: Table S5). The patients of cluster 4 were prone to disease progression (HR 2.711, 95% CI 1.128–6.519, *P* = 0.026) after adjusted for age, sex and smoking status by multivariable Cox proportional hazards model, which was in line with the Kaplan–Meier curves (Table 4).

Table 4
Multivariable Cox proportional hazards model for interstitial pneumonia progression or death

Variables	*P value*	HR	95% CI of HR
Female	0.683	0.839	0.362–1.946
Age*	0.502	1.009	0.983–1.036
Non-smokers#	0.524		
Current smokers	0.337	0.585	0.196–1.749
Ex-smokers	0.310	0.593	0.217–1.626
Cluster&	0.035		
Cluster 2	0.367	1.436	0.654–3.152
Cluster 3	0.291	0.514	0.150–1.767
Cluster 4	0.026	2.711	1.128–6.519
*, age at the diagnosis; #, take non-smokers as a reference; &, take cluster1 as a reference.			
Abbreviations: HR, hazard ratio.			

Discussion

The present study is the first report of using cluster analysis to classify the MSA-IP patients into four distinctive clusters i.e. cluster 1, elders with UIP pattern; cluster 2, patients with pulmonary symptoms and anti-ARS; cluster 3, patients with multi-system involvements, acute onset, and NSIP pattern; cluster 4, patients with acute onset, disease progression and anti-MDA5. The classification of patients was based on clinical features, autoantibodies and prognosis.

Previous studies had indicated the potential importance of MSA in the diagnosis and prognosis of IP. 26.7% (44/165) of patients with IP on their initial diagnosis were positive for myositis autoantibodies [32]. The overall survival of IP with anti-ARS was higher than that of idiopathic pulmonary fibrosis (IPF). However, no difference of overall survival was found between IP patients with anti-ARS who can be diagnosed IIM or not [20]. Previous studies indicate that the evaluation of MSA is more valuable for recognition and management of IP patients than the diagnosis of IIMs [20, 33, 34]. According to the ERS/ATS statement, some of the MSA-IP patients who did not meet the criteria of IIMs can be diagnosed as IPAF [5]. However, compared with MSA-IP, the entity of IPAF is more heterogeneous and the diagnosis of IPAF may lead to delayed clinical intervention [35]. In this study, we chose MSA-IP patients as the study population for cluster analysis.

In cluster 1, UIP pattern on HRCT was observed in all patients. A spectrum of ILDs present UIP pattern, and the three most common diseases are IPF, rheumatic ILD (RILD) and chronic hypersensitivity pneumonitis (CHP) [36]. The histopathological features of these diseases with UIP pattern are different. There are spatial and temporal heterogeneity, fibroblastic foci, peripheral lobular distribution, microscopic honeycomb in IPF; airway-centered fibrosis, NSIP-like alveolar septal fibrosis, follicular bronchiolitis, pleural fibrosis in RILD; and patchy fibrosis along the bronchovascular bundle with rare fibroblast foci, honeycomb cysts in upper and lower lobes, extensive peribronchiolar metaplasia, bridging fibrosis across lobules in CHP [36]. The mean survival time of RILD with UIP is longer than IPF with UIP [37]. Progressive-fibrosing ILDs (PF-ILDs) refer to fibrotic ILDs that present progressive phenotypes with multiple causes whose clinical, radiological and pathological characteristics overlap with IPF [38]. UIP pattern is the representation of irreversible pulmonary fibrosis and indicates a poor prognosis [39] so that ILDs with UIP pattern is in the category of PF-ILD [40]. Given the similarities in pathogenesis of fibrosis, the results of a clinical trial showed that Nintedanib can reduce the annual decline rate of FVC in PF-ILD [40]. In our study, the MSA-IP patients of cluster 1 have UIP pattern indicating the clinicians to differentiate UIP pattern of possible MSA-IP, especially cluster 1. In addition, antifibrotic drug may also be valuable in MSA-IP patients of cluster 1 [39].

All patients of cluster 2 were positive for anti-ARS, in which anti-Jo-1 and anti-EJ were common, and were characterized by respiratory symptoms and NSIP pattern. In cluster 3, anti-Jo-1 and anti-PL-7 were the major MSA subtypes, and patients had multi-system involvements. NSIP pattern and acute onset were also features of cluster 3. NSIP is the most common pathological and radiological features of anti-synthetase syndrome (ASS) presenting myositis, IP, arthritis, mechanic's hands, Raynaud's phenomenon and fever [41, 42]. Patients with ASS have relatively common clinical features, but the subtype of anti-ARS indicates certain clinical subset and predicates complications [41]. A previous study reported that the patients with anti-Jo-1, anti-EJ and anti-PL-7 were prone to occur myositis following ILDs [41]. However, the patients with various anti-ARS are not able to be distinguished by HRCT patterns of IPs.

Cluster 4 patients had dyspnea, decreased oxygenation and AIP pattern. Anti-MDA5, acute onset and susceptibility to disease progression were representative features in cluster 4. Among DM patients in the U.S. and Japan, 13.1–37.3% were positive for anti-MDA5 [43, 44]. Anti-MDA5 was found to be associated with rapidly progressive ILD and poor survival with mortality as high as 71.4% [43]. The initial triple therapy, including high-dose prednisolone, calcineurin inhibitor and intravenous cyclophosphamide were commonly used in survivors of rapidly progressive ILD with anti-MDA5 than in non-survivors, indicating that initial triple therapy may improve prognosis of these patients [44]. For IP patients with anti-MDA5 who failed to respond to triple therapy, combined treatment with Tofacitinib might be beneficial in controlling disease progression [45]. The detection of anti-MDA5 contributes to risk stratification. One study suggested that patients presenting with rapidly progressive IP should be detected with autoantibodies to increase diagnostic sensitivity [35].

Several limitations of this study should be considered. First, selection bias might exist because the enrolled patients did not fully represent the diversity of organ involvements in MSA-IP as they were

derived from a single medical center. Second, the clustering variables did not contain therapeutic data. In this study, MSA-IP patients were mainly treated with corticosteroid and immunosuppressive agents including cyclophosphamide, methotrexate, azathioprine, mycophenolate mofetil, cyclosporine, or hydroxychloroquine, with or without antifibrotic therapy. Finally, the follow-up period was limited for observing disease progression of the patients. The prospective long-term longitudinal research is warranted to verify the four clusters of MSA-IP patients in this study.

Conclusions

We applied cluster analysis in MSA-IP for the first time resulting in the categorization of four clusters. The results indicated that MSA play a key role in clinical representation, disease onset and prognosis of IP. These results may help to recognize MSA-IP patients and develop individualized regimens. Further studies are needed to explore the correlation in clinical characteristics with underlying genetic mechanisms of corresponding MSA subtypes .

Abbreviations

ACR, American College of Rheumatology; ADM, amyopathic dermatomyositis; AIP, acute interstitial pneumonia; anti-ARS, anti-aminoacyl-tRNA-synthetase antibodies; ASS, anti-synthetase syndrome; ATS, American Thoracic Society; CHP, chronic hypersensitivity pneumonitis; CTDs, connective tissue diseases; CTD-ILD, CTD-associated ILD; DLCO, diffusing capacity of the lung for carbon monoxide; DM, dermatomyositis; ERS, European Respiratory Society; EULAR, European League Against Rheumatism; FVC, forced vital capacity; HRCT, high-resolution computed tomography; Ig, immunoglobulin; IIM, idiopathic inflammatory myopathy; IIPs, idiopathic interstitial pneumonias; ILDs, Interstitial lung diseases; IP, interstitial pneumonia; IPAF, interstitial pneumonia with autoimmune features; IPF, idiopathic pulmonary fibrosis; MAA, myositis-associated autoantibodies; MSA, myositis-specific autoantibodies; MSA-IP, interstitial pneumonia patients with MSA; NSIP, nonspecific interstitial pneumonia; PF-ILDs, progressive-fibrosing ILDs; PM, polymyositis; RILD, rheumatic ILD; UIP, usual interstitial pneumonia.

Declarations

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Ethics approval and consent participate

The protocol of the prospective study was approved by the Institutional Review Board of Beijing Chao-Yang Hospital. Informed consents were obtained from all patients.

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Availability of data and materials

The datasets used in the current study are available from the corresponding author upon reasonable request.

Author's contributions

YH Li was responsible for completing the analysis of data and writing. SW Yu and YL Fan performed all data collection. N Wu and YR Wang were responsible for recruiting the patients and collecting plasma samples. Q Ye contributed as primary investigator and was responsible for designing the study, recruiting the patients and writing the manuscript. All authors have read and approved the final manuscript.

Consent for publication

Not applicable.

Competing Interests

The authors have no conflicts of interest to declare.

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Figures

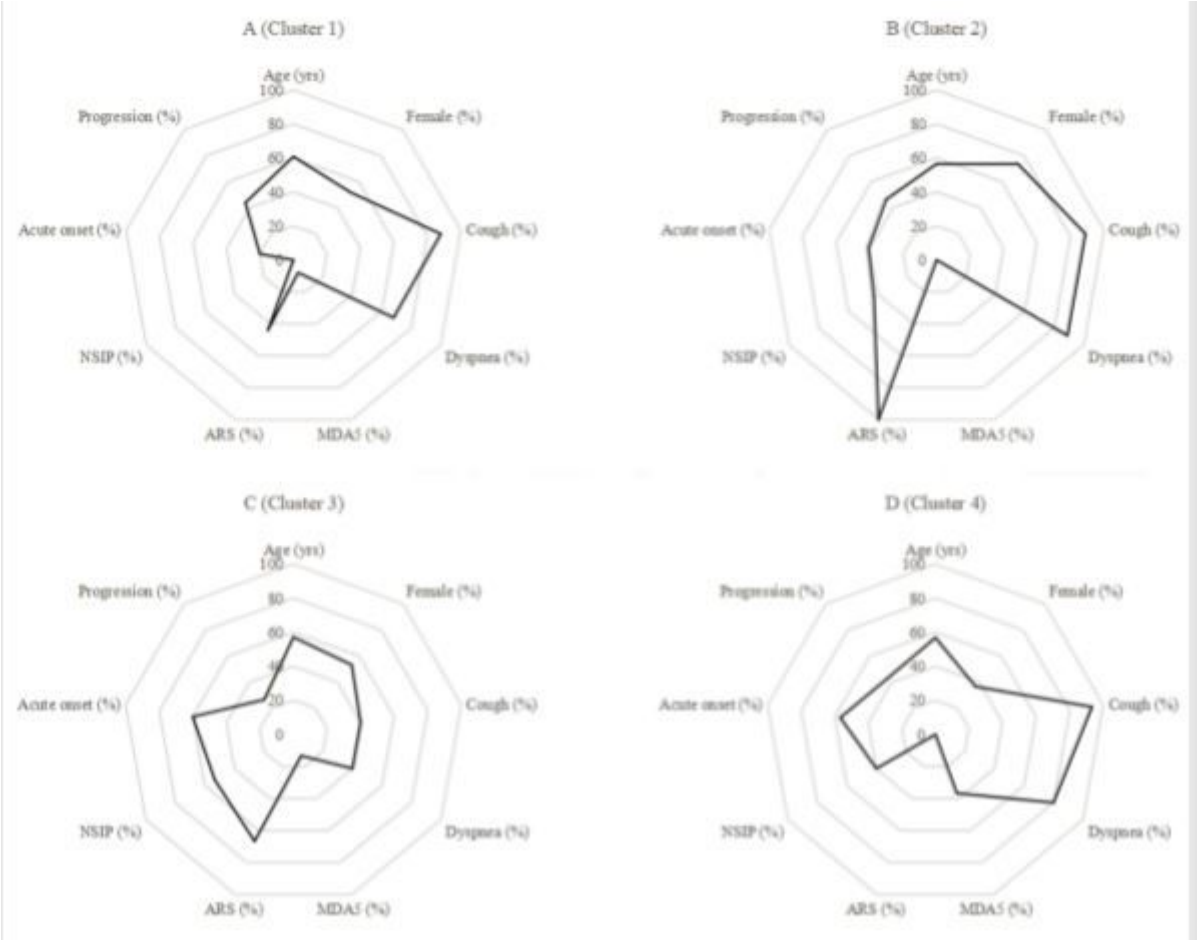

Figure 1

Radar plot depicting the distribution of demographics, clinical characteristics, MSA subtypes and HRCT findings among four clusters. %, the percentage of patients with corresponding characteristics; yrs, age at diagnosis.

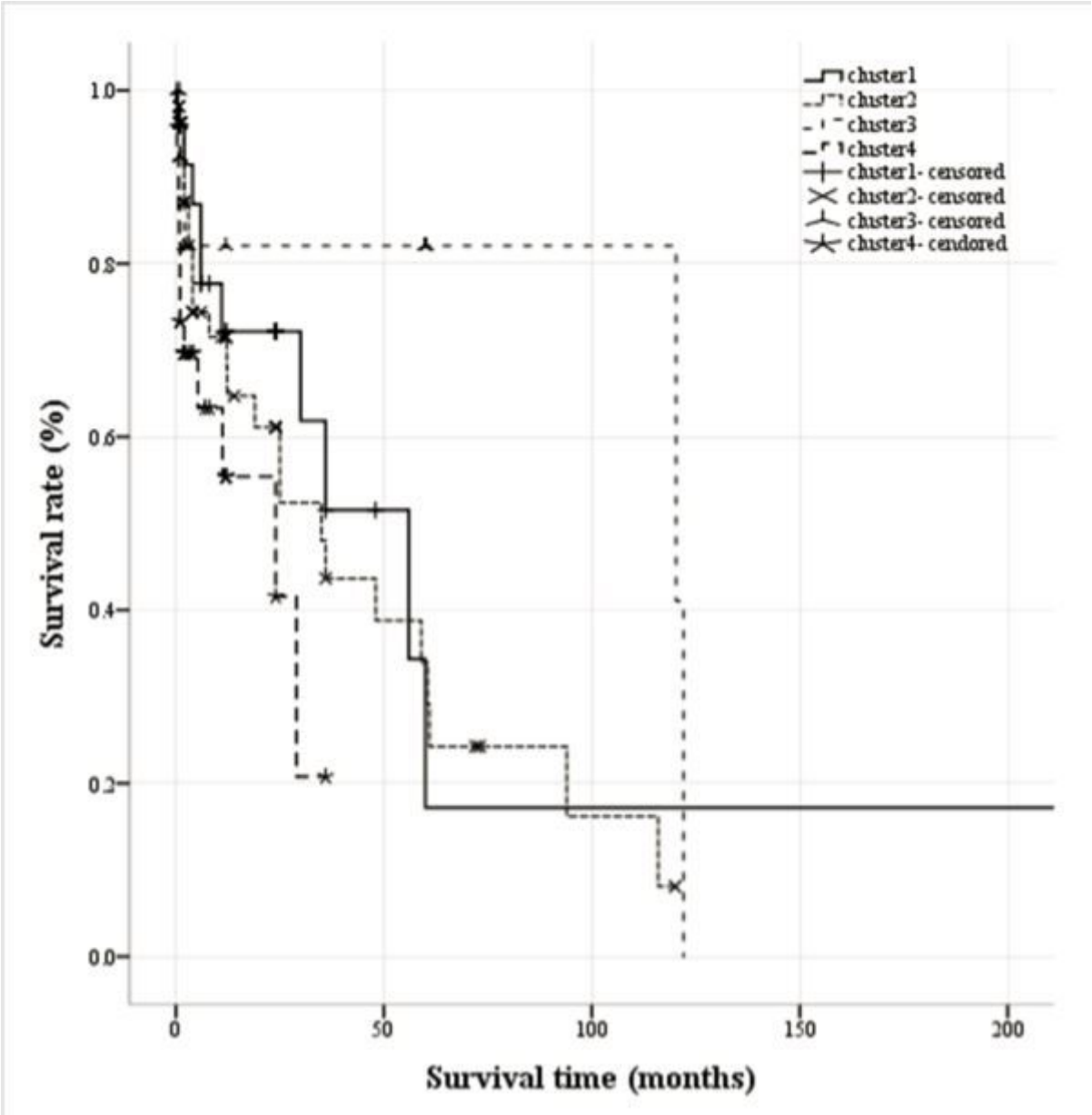

Figure 2

Kaplan–Meier curves of MSA-IP patients in four clusters (cluster 1, solid line; cluster 2, dotted line; cluster 3, short dashed line; cluster 4, long dashed line). Survival time was calculated from the onset of symptoms to outcomes or the end of the follow-up period. The median survival time of all patients was 36 months (range, 0.1-360 months). The median survival time of cluster 4 was 24 months, which was the shortest. The prognosis of cluster 4 patients was the worst among all other clusters (χ2=9.138, log rank P=0.028).

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