Clinical features of idiopathic inflammatory myopathies with infection based on a cluster analysis

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Abstract

Objectives.

Patients with idiopathic inflammatory myopathies (IIM), referred to as myositis, are prone to infectious complications, which hinder the treatment of the disease and worsen the outcome of patients. The purpose of this study was to explore the different types of infectious complications in patients with myositis and to determine the predisposing factors for clinical reference.

Methods.

A retrospective study was conducted on 66 patients with IIM who were divided into different types by an unsupervised analysis of their clinical manifestations, laboratory features, and autoantibody characteristics. Combined with the incidence of infectious complications, the types of infectious pathogens and the sites of infection, the characteristics of infection and susceptibility factors were explored.

Results.

Three clusters with significantly different clinical characteristics and coinfection rates were identified (76.2% vs. 41.6% vs. 36.4%, p=0.0139). Cluster 1 (n = 12) had a moderate risk of infection, with an infection rate of 41.6%. The patients in cluster 1 had a high probability of positive mechanic's hands, periungual erythema, anti-Ro52 antibody, and anti-Jo1 antibody. CD3 and CD4 were the highest among the three groups. Cluster 2 (n = 21) had a high risk of infection, and the incidence of infection was 76.2%. Almost all patients in this cluster had a rash, prominent clinical symptoms, and decreased WBC, PMN, LYM, CD3 and CD4 counts. Cluster 3 (n=33) had a low risk of infection, with an infection rate of 36.4%. Compared with the other two clusters, cluster 3 (n=33) lacked a typical rash but had a high ANA positive rate. The patients in cluster 1 and cluster 3 were mainly infected by viruses, followed by bacterial infections. In the cluster 2 patients, bacterial infections were the most prevalent. Fungal and Pneumocystis carinii were common causes of cluster 2 and 3 infections. In addition, the patients within a cluster often have a single infection, and pulmonary infections are the most common.

Conclusion.

We clustered the patients with IIM complicated with infection into three different types by their clinical symptoms and found that there were differences in the infection risk and infection types among the different cluster groups.

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Introduction
Idiopathic inflammatory myopathies (IIM) are a heterogeneous group of inflammatory myopathies referred to as myositis. Their common feature is immune-mediated muscle injury. According to their pathological characteristics, they are divided into dermatomyositis (DM), immune-mediated necrotizing myopathy (IMNM), dermatomyositis (DM), sporadic inclusion body myositis, and polymyositis (PM) [1]. The symptoms of the different types of myositis mainly include muscle weakness in the arms and legs that limits daily activities, multiple rashes (most notably on the hands), accompanied by pain, and a significant increase in creatine kinase (CK), often 10–50 times the normal range, over a period of several days to several weeks. Anti-melanoma differentiation-associated gene 5 (anti-MDA5), anti-Ro52, anti-Jo1 and other autoantibodies are usually abnormal[2]. Myositis can also affect multiple organs in addition to the muscles and often leads to severe impairment in quality of life[3]. The multiversion clinical diagnostic criteria often combine clinical symptoms, antibody and laboratory test results, and even biopsy results to make a comprehensive diagnosis of myositis[4]. In terms of incidence, all forms of myositis are considered rare diseases. Although DM is the most common myopathy, it affects only 1–6 people per 100,000 in the United States[5]. However, the decreased quality of life, physical impairment, and increased mortality due to myositis are not negligible.

Infection is one of the most common complications in patients with myositis. It has been reported that up to 26% of patients have infectious complications, including skin infections, respiratory tract infections, urinary tract infections, etc. Complications lead to increased hospitalization and mortality in patients with myositis [5][6]. Therefore, we should pay attention to infectious complications in patients with myositis. At present, it is believed that there are some predisposing factors in patients with myositis complicated with multiple infections, such as the degree of disease activity and drug use regimen[7]. However, the specific diagnostic criteria and classification criteria of infectious comorbidities and the possible precipitating factors of different infections are still not very clear. This brings challenges for clinical prevention, timely detection and appropriate treatment of infectious comorbidities in patients with myositis.

Therefore, in this study, we collected the clinical data of patients with myositis complicated with infection; classified the patients by combining the clinical symptoms, autoantibody changes, and laboratory test results; sorted out and summarized the pathogen types and infection sites of patients with different classifications of myositis complicated with infection; and explored the predisposing factors of different types of infections in patients with myositis to help improve the understanding of myositis patients with infection and provide relevant reference information for clinical practice.

**Methods**

**Patient selection**

We retrospectively analyzed 66 patients diagnosed with IIM from the Department of Rheumatology in West China Hospital of Sichuan University between January 2020 and January 2021. All patients met the Bohan and Peter criteria for IIM classification[8]. The infection status of all patients was comprehensively
analyzed. Patients with malignant disease and other connective tissue were excluded. The study was approved by the ethical committee of West China Hospital of Sichuan University (No. 695 in 2020) and complied with the Declaration of Helsinki.

**Collection Of Clinical Features**

The patients’ medical charts were retrospectively reviewed for demographic characteristics, clinical features, and laboratory data. The data collected included age, sex, duration of IIM, clinical symptoms and signs, routine blood parameters, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, creatine kinase (CK), lactate dehydrogenase (LDH), hydroxybutyrate dehydrogenase (HBDH), myoglobin protein (MYO), as well as immunological indicators such as immunoglobulin (Ig), complement (C), T-cell subpopulation count (CD3+, CD4+, CD8+), antinuclear antibodies (ANA), anti-Ro52 antibody, and myositis specific antibodies.

**The Definition Of Infections**

A positive pathogenic microbiological result, such as a positive test on blood, urine, sputum, bronchoalveolar lavage fluid, or tissue culture, and corresponding clinical symptoms and imaging examinations were defined as coinfection.

**Cluster Analysis Methodology**

We used the Manhattan distance to comprehensively evaluate the absolute distances between individual patient samples from multiple features, summed them, and then compared the degree of similarity between the individual samples [9]. Larger distances indicate greater differences, and smaller distances indicate greater similarity. The characteristics of our cluster analysis included variables that may be useful for disease classification and are highly correlated with infection. Four clinical features with more than 10% deletion were deleted, including ferritin, B-cell count, IL-6, and immunoglobulin E. Patients with missing data were excluded prior to analysis. The Manhattan distance between the sample points was used to merge with complete linkage, that is, the longest node in the two sample points was used as the distance of the sample points, and the sample point with the smallest difference between the groups was selected to merge into a new sample. Then, the above operation was repeated until all the samples were merged into one sample. The contour coefficient was used to evaluate the clustering effect[10]. The value of the contour coefficient was closer to 1, indicating that both cohesion and separation were relatively better. Finally, the patients were divided into three clusters, and their clustering was displayed by dendrogram (Fig. 1). This is a kind of binary tree graph, the abscissa is the sample, and the ordinate represents the distance. The larger the distance is, the more significant the difference between the clusters. In contrast, if the distance is small, the difference is not obvious.

**Statistical Analysis.**
Characteristics were compared among the clusters using the chi-square, ANOVA and Kruskal–Wallis tests as appropriate. Cluster analysis was performed using R version 3.6.3.

**Result**

**Clinical subgroups by cluster analysis.**

We sought to classify clinically relevant subgroups among IIM patients with infection and to identify the clinical manifestations associated with infection. Therefore, a total of 66 patients were included in the cluster analysis. The patients were divided into phenotypes based on an unsupervised cluster analysis. Data from 66 patients (45 women and 21 men) with 50 variables were described. We further removed the samples with significant missing data, and 46 variables were finally entered into the unsupervised analysis. The patients were classified into three groups by cluster analysis (Fig. 1). The clinical features of each cluster are shown in Table 1. The clinical characteristics of the 3 clusters are summarized in Fig. 2.
Table 1
Clusters by partitioning around medoids cluster analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cluster</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 (n = 12)</td>
<td>2 (n = 21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>General information</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>2(17)</td>
<td>7(33)</td>
</tr>
<tr>
<td>Age, Mean ± SD, years</td>
<td>50.08 ± 11.81</td>
<td>45.38 ± 12.32</td>
</tr>
<tr>
<td>Disease course, Mean ± SD, months</td>
<td>21.75 ± 24.54</td>
<td>13.86 ± 28.78</td>
</tr>
<tr>
<td>BMI, Mean ± SD, kg/m²</td>
<td>23.6 ± 3.224</td>
<td>20.71 ± 6.063</td>
</tr>
<tr>
<td><strong>Clinical manifestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever, n (%)</td>
<td>1(8)</td>
<td>8(38)</td>
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<tr>
<td>Cough, n (%)</td>
<td>9(75)</td>
<td>7(33)</td>
</tr>
<tr>
<td>Expectoration, n (%)</td>
<td>5(42)</td>
<td>7(33)</td>
</tr>
<tr>
<td>Dyspnea, n (%)</td>
<td>7(58)</td>
<td>13(62)</td>
</tr>
<tr>
<td>Arthritis, n (%)</td>
<td>6(50)</td>
<td>12(57)</td>
</tr>
<tr>
<td>Myalgia, n (%)</td>
<td>2(17)</td>
<td>11(52)</td>
</tr>
<tr>
<td>Myasthenia, n (%)</td>
<td>4(33)</td>
<td>20(95)</td>
</tr>
<tr>
<td>Rash, n (%)</td>
<td>5(42)</td>
<td>21(100)</td>
</tr>
<tr>
<td>Heliotrope rash, n (%)</td>
<td>3(25)</td>
<td>18(86)</td>
</tr>
<tr>
<td>&quot;V&quot; sign, n (%)</td>
<td>3(25)</td>
<td>15(71)</td>
</tr>
<tr>
<td>Gottron papule, n (%)</td>
<td>4(33)</td>
<td>18(86)</td>
</tr>
<tr>
<td>Mechanic’s hands, n (%)</td>
<td>5(42)</td>
<td>2(10)</td>
</tr>
<tr>
<td>Periungual erythema, n (%)</td>
<td>3(25)</td>
<td>1(5)</td>
</tr>
<tr>
<td>Moist, n (%)</td>
<td>1(8)</td>
<td>6(29)</td>
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<td><strong>Laboratory features</strong></td>
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<td></td>
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<tr>
<td>HGB, Mean ± SD</td>
<td>128.5 ± 11.46</td>
<td>120.1 ± 23.02</td>
</tr>
<tr>
<td>Variable</td>
<td>Cluster 1 (n = 12)</td>
<td>Cluster 2 (n = 21)</td>
</tr>
<tr>
<td>------------------------</td>
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<td>-------------------</td>
</tr>
<tr>
<td>PLT, Mean ± SD</td>
<td>220.3 ± 83.41</td>
<td>173.8 ± 66.96</td>
</tr>
<tr>
<td>WBC, Mean ± SD</td>
<td>7.084 ± 2.209</td>
<td>5.834 ± 2.070</td>
</tr>
<tr>
<td>PMN, Mean ± SD</td>
<td>5.019 ± 1.874</td>
<td>4.346 ± 1.726</td>
</tr>
<tr>
<td>LYM, Mean ± SD</td>
<td>1.403 ± 0.639</td>
<td>0.841 ± 0.328</td>
</tr>
<tr>
<td>MONO, Mean ± SD</td>
<td>0.552 ± 0.219</td>
<td>0.513 ± 0.276</td>
</tr>
<tr>
<td>CD3, Mean ± SD</td>
<td>1001 ± 203.2</td>
<td>565.7 ± 283.9</td>
</tr>
<tr>
<td>CD4, Mean ± SD</td>
<td>589.4 ± 152.5</td>
<td>307.9 ± 176.4</td>
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<tr>
<td>CD8, Mean ± SD</td>
<td>384 ± 172.5</td>
<td>235.3 ± 160.6</td>
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<tr>
<td>ALT, Mean ± SD</td>
<td>25.08 ± 13.76</td>
<td>46.24 ± 38.63</td>
</tr>
<tr>
<td>AST, Mean ± SD</td>
<td>25.08 ± 11.45</td>
<td>59.14 ± 39.11</td>
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<tr>
<td>CK, Mean ± SD</td>
<td>170.1 ± 266.8</td>
<td>269 ± 864.7</td>
</tr>
<tr>
<td>LDH, Mean ± SD</td>
<td>238.7 ± 47.22</td>
<td>368.5 ± 144.4</td>
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<tr>
<td>HBDH, Mean ± SD</td>
<td>184.3 ± 32.47</td>
<td>287.6 ± 110.5</td>
</tr>
<tr>
<td>MYO, Mean ± SD</td>
<td>136.6 ± 219.6</td>
<td>161.2 ± 361.8</td>
</tr>
<tr>
<td>CK-MB, Mean ± SD</td>
<td>3.975 ± 4.899</td>
<td>6.879 ± 16.06</td>
</tr>
<tr>
<td>IgG, Mean ± SD</td>
<td>10.56 ± 3.208</td>
<td>14.71 ± 5.54</td>
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<td>IgA, Mean ± SD</td>
<td>1999 ± 894.4</td>
<td>2537 ± 1099</td>
</tr>
<tr>
<td>IgM, Mean ± SD</td>
<td>1440 ± 656</td>
<td>1641 ± 765</td>
</tr>
<tr>
<td>C3, Mean ± SD</td>
<td>0.9002 ± 0.094</td>
<td>0.8214 ± 0.175</td>
</tr>
<tr>
<td>C4, Mean ± SD</td>
<td>0.2115 ± 0.076</td>
<td>0.2448 ± 0.097</td>
</tr>
<tr>
<td>ESR, Mean ± SD</td>
<td>34.10 ± 25.77</td>
<td>43.70 ± 23.97</td>
</tr>
<tr>
<td>CRP, Mean ± SD</td>
<td>11.72 ± 15.68</td>
<td>9.935 ± 11.01</td>
</tr>
</tbody>
</table>

**Autoantibody**

<table>
<thead>
<tr>
<th>ANA, positive, n (%)</th>
<th>10(83)</th>
<th>12(57)</th>
<th>25(76)</th>
<th>0.1999</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Ro52 antibody, positive, n (%)</td>
<td>12(100)</td>
<td>11(52)</td>
<td>16(48)</td>
<td>0.0060**</td>
</tr>
<tr>
<td>Variable</td>
<td>Cluster 1 (n = 12)</td>
<td>Cluster 2 (n = 21)</td>
<td>Cluster 3 (n = 33)</td>
<td>p Value</td>
</tr>
<tr>
<td>--------------------------------</td>
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<td>-----------------</td>
</tr>
<tr>
<td>Anti-MDA5 antibody, positive, n (%)</td>
<td>3(25)</td>
<td>14(67)</td>
<td>1(3)</td>
<td>&lt; 0.0001****</td>
</tr>
<tr>
<td>Anti-Jo1 antibody, positive, n (%)</td>
<td>6(50)</td>
<td>0(0)</td>
<td>5(15)</td>
<td>0.001**</td>
</tr>
<tr>
<td>Prognosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection, n (%)</td>
<td>5(42)</td>
<td>16(76)</td>
<td>12(36)</td>
<td>0.0139*</td>
</tr>
</tbody>
</table>

*Indicates statistical difference between three clusters, *P<0.05, **P<0.005, ***P<0.0005, ****P<0.0001.

**Abbreviations:**

HGB, Hemoglobin; PLT, platelet; WBC, White blood cell; PMN, polymorphonuclear neutrophils; LYM, lymphocytes; MONO, monocytes; IgG, immunoglobulin G; IgM, immunoglobulin M; IgA, immunoglobulin A; C3, Complement 3; C4, Complement 4; LDH, lactate dehydrogenase; HBDH, hydroxybutyrate dehydrogenase; MYO, myoglobin; CK-MB, creatinine kinase MB; ALT, alanine transaminase; AST, aspartate aminotransferase; CK, creatine kinase; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ANA, antinuclear antibody; Ro52, anti-cytoplasmic ribonucleoprotein of 52 kDa; MDA5, Melanoma differentiation-associated gene 5; anti-Jo1 antibody, anti–histidyl-ARN-t- synthetase antibody.

The patients in Cluster 1 (n = 12; 18.2%) had moderate infection features (moderate-risk cluster), among whom 5 patients (41.6%) had infections. This cluster's features were obvious mechanic's hands (41.6% vs. 9.5% vs. 3.0%), periungual erythema (25.0% vs. 4.8% vs. 0%), and rarely fever (8.3% vs. 22.3% vs. 12.1%) and myasthenia (33.3% vs. 95.2% vs. 84.9%), as compared with the other two clusters. Among the 3 clusters, this cluster's patients were more likely to have the lowest ALT, AST, CK, LDH, HBDH, MYO, and CK-MB levels and the highest anti-Ro52 antibody and anti-Jo1 antibody positive rates. Meanwhile, cluster 1 was accompanied by the highest numbers of CD3 and CD4.

The patients in Cluster 2 (n = 21; 31.8%) had high infection features (high-risk cluster), among whom 16 patients (76.2%) had infections. Almost all the patients in cluster 2 complained of rashes, and the rashes included heliotrope rashes (25% vs. 85.7% vs. 12.1%), “V” sign (25% vs. 71.4% vs. 6.1%), and Gottron papules (33.3% vs. 85.7% vs. 12.1%). Signs of fever and myasthenia were frequent in this group, and this group had a high percentage of anti-MDA5 antibody positive patients. In addition, most patients had decreased WBC, PMN, LYM, CD3, CD4 and anti-JO1 antibody-positive levels.

The patients in Cluster 1 (n = 33; 50%) had low infection features (low-risk cluster), among whom 12 patients (36.4%) had infections. Compared with clusters 1 and 2, this cluster infrequently had accompanying DM-typical rashes of any kind, including the heliotrope rash, “V” sign, Gottron papule, mechanic's hands and periungual erythema. Meanwhile, anti-Ro52 antibodies and anti-MDA5 antibodies
were also rare in the cluster 3 patients. However, this cluster has a high rate of ANA antibody positivity and high levels of ALT, AST, CK, LDH, HBDH, MYO, CK-MB, WBC, LYM, and PMN.

**Infection features of the patients in different clusters.**

We next analyzed the prevalence of infection in the 3 clusters (Fig. 2A). We found significant differences in the infection rate among the 3 groups. The patients in cluster 2 had a very high infection rate compared to the patients in the other two clusters (76.2% vs. 41.6% vs. 36.4%, $p = 0.0139$). The common infections in the three clusters of patients included viral, bacterial, fungal, mycoplasma, tuberculosis, and pneumocystis carinii infections. The patients in clusters 1 and 3 commonly had viral infections, followed by bacterial infections. Bacterial infection was the most common infection type in the cluster 2 patients (Fig. 2B). Meanwhile, fungi and *Pneumocystis carinii* were the common causes of infections in clusters 2 and 3. The patients in the 3 clusters often exhibited single infections rather than mixed infections (Fig. 2C). Of the 33 patients, 72.7% of the patients showed evidence of pulmonary infections, 9.1% had urinary tract infections, and 21.2% had uncertain site infections. Pulmonary infections were the most common infections in IIM patients (Fig. 2D).

**Discussion**

Infectious diseases are a major cause of mortality in patients with connective tissue disease[11], and a large proportion of deaths in IIM patients are attributed to complications of infection[12]. Therefore, discriminating IIM patients who are at risk is beneficial to prevent severe infection and reduce mortality. We clustered the patients with IIM complicated with infection into three different types by their clinical symptoms and found that there were differences in infection risk and infection types among the different cluster groups, showing the potential role of analysis by cluster trend.

This study found three subgroups with a distinct pattern of symptoms among patients with IIM. The patients were divided into a moderate-risk group (cluster 1), a high-risk group (cluster 2) and a low-risk group (cluster 3). The patients in the high-risk group reported higher fever, myasthenia and rash. Fever and myasthenia are the main clinical manifestations associated with infection, as well as indicators of IIM disease activity (such as MYOACT MITAX), so disease-related immune dysregulation, high doses of glucocorticoids and immunosuppressant drugs were responsible for the increased frequency of infections in these patients. Similarly, rashes are an indicator of myositis disease activity. Gottron papule, heliotrope rash and V sign are the prominent characteristics of DM[13]. A single-center study involving 779 patients with IIM found that infection was more common in patients with dermatomyositis than in those with polymyositis, and they also found that a heliotrope rash is a risk factor for infection[14]. This finding supported symptom status as a key predictor of infection.

The positive rate of anti-MDA5 antibody was higher in the high-risk group. Anti-MDA5 antibody-positive myositis is a class of dermatomyositis characterized by light muscle involvement and serious lung involvement, with rapidly progressive pulmonary interstitial fibrosis, often resulting in death. Our study identified anti-MDA5 antibodies as a risk factor for developing infection, which was supported by a
previous study [15]. This may be because anti-MDA5 antibody-positive patients often have pulmonary interstitial fibrosis, a breakdown of the lung defense barrier, and thus an increased risk of infection. Several studies have indicated that ILD is an independent risk factor for infection. [14][15] Interestingly, we found a reduced risk of infection in patients who were positive for anti-Jo1 antibodies. This was consistent with the research of Yongpeng et al [14]. However, another study suggested otherwise [15]. Therefore, the relationship between positive anti-JO1 antibodies and infection needs further investigation.

Consistent with previous findings, the patients in the high-risk group had lower lymphocyte counts. This finding suggests that lymphocytopenia is an effective predictor of infection. The relative contributions of T lymphocyte cells during bacterial infections have been investigated extensively. Various antigens act as signals to stimulate naive T cells, which activate and multiply to produce effector T cells, thus enabling the elimination of infectious pathogens. [16][17]. Lymphocytopenia is generally recognized as an independent risk factor for developing serious infections, including opportunistic infections [14][15]. Meanwhile, lymphocytopenia is a prominent characteristic in patients with active dermatomyositis, and this also supports the conclusion that the patients with rash in our cohort had a higher frequency of infection [18]. In addition, a higher frequency of infection was observed in IIM patients with neutropenia in our cohort. Neutrophils are the most abundant immune cells in humans and are the first line of defense against outside microbes; low neutrophil counts often occur in patients with aggressive fungal infections. [19] Therefore, it is necessary to pay attention to the number of lymphocytes and neutrophils in the peripheral blood of patients with IIM to detect and prevent infection in time.

In clinical practice, CRP, ESR, and Moist are used to determine whether there is infection; however, no differences were found between clusters 2 and 3. These findings led to the conclusion that CRP, ESR and Moist did not directly reflect infection. Higher levels of CK, LDH, HBDH, ALT, and AST tended to appear in the low-risk group, indicating a lower risk of infection in patients with severe muscle involvement, i.e., immune-mediated necrotizing myopathy.

In addition, we analyzed the characteristics of infection in IIM patients and found that the lungs are the most common site of infection in IIM patients, followed by the urinary tract. IIM patients often develop pulmonary interstitial fibrosis, which leads to a breakdown of the pulmonary mucosal barrier and makes the lungs susceptible to pathogenic microorganism invasion. This is consistent with the conclusions of many previous studies [15][20][21]. Bacterial infections are the most common type of infection in IIM patients, followed by viruses and fungi. Two studies of IIM infection found ratios of fungi vs. viruses vs. fungi of 55 vs. 6 vs. 3 and 39 vs. 3 vs. 10, respectively. [15][22]. The proportion in our cohort was 19:13:6, and the rate of viral infections increased significantly. This may be due to the development of viral infection detection technology, which increased the diagnosis rate of viral infections. The common viral infections in our cohort included Epstein–Barr virus, cytomegalovirus, and herpes simplex virus. Studies have reported that CMV is the most common type of IIM virus infection, and a Chinese study showed increased mortality from CMV coinfection [23]. In addition, pneumocystis infection was also seen in patients with IIM. Prevention of Pneumocystis carinii pneumonia is extremely important to improve patient outcomes because opportunistic infections are common in patients with CTD with
immunosuppression, and connective tissue diseases associated with *Pneumocystis carinii* infection have a high mortality rate of 33–60%[24]. Previous studies have shown that decreased CD4 lymphocyte counts, duration and dose of glucocorticoids, and ILD were risk factors for *Pneumocystis carinii* infection[24]. A meta-analysis showed that the prevalence rate of MTB infection in IIM was 3.58%[25]. In our study, there was only 1 case of MTB infection in IIM patients (1.52%), which was lower than previous studies, and this may be due to the limited number of patients in our study. In conclusion, patients with IIMs have complications, and infections are not uncommon. Understanding the specific risk of IIM infection is beneficial to prevent serious complications and improve the survival rate of IIM.

The limitations of this study include the following: (1) the sample size of this study is small, and a larger cohort of IIM patients is needed to replicate and verify the existing conclusions. (2) This is a retrospective study with unavoidable limitations, such as bias in information recall and case selection. (3) This was a single-center study with a relatively single population, and (4) there was a subjective factor in the feature selection for cluster analysis. Although we screened a wide range of clinical parameters for clustering, we could not prove whether other clinical features contributed to the occurrence of infection. (5) Regarding the results of the cluster analysis, there was a lack of validation in the development and external validation cohorts.

**Conclusion**

Patients with IIM complicated with infection could be clustered into three different types according to their clinical characteristics, and the risk and characteristics of infection were different among the different clusters. Coinfection in IIM patients mainly involves viral and bacterial single infections. Fungi and *Pneumocystis carinii* are common pathogens, and pulmonary infection is the most common. This study provides a reference for the prevention and management of infectious complications in IIM patients and helps doctors closely follow up with high-risk patients and treat them in a timely manner.

**Declarations**

**Ethics approval and consent to participate**

The study was approved by the ethical committee of West China Hospital of Sichuan University (No. 695 in 2020) and complied with the Declaration of Helsinki. The study did not involve animal studies, that no ethical approval is required.

**Consent for publication**

All patients and controls provided written informed consent.

**Availability of data**

The data supporting the conclusions of this article are included within the article and its additional file.
Competing interests

All authors declare that they have no conflict of interest.

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Authors' information

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Authors' contributions

LY, TCY, and LYB conceived and designed the study. LY and TCY guided the study. CL, LYH, WYL, ZY, LZH, WJ, LXP, and WT collected the clinical samples. CL, LYH, WYL, analyzed the data. All authors drafted and revised the manuscript. All authors drafted and revised the manuscript. Lu Cheng and Yanhong Li contributed equally to this work.

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References


Figures
Figure 1

Unsupervised analysis of IIM patients

The hierarchical cluster analysis of IIM patients showed 3 clusters

Figure 2

The different clinical presentations in the three clusters.

A. The heatmap shows differences in clinical manifestations among the three clusters, and the difference was statistically significant (p<0.05). The patients in three clusters with the smallest frequency clinical variables or continuous values are indicated in green, while the patients with the most frequency clinical
variables or continuous values are indicated in red. The heatmap shows the relative minimum (green, 1) and maximum (red, 20) values per row.

B. Schematic diagram displaying the different clinical phenotypes, antibody positivity rates and laboratory features of patients among the three clusters.

“+” low positivity rate, “++” moderate positivity rate, “+++” strong positivity rate

Figure 3

Proportions of infection and infection features of patients in three clusters

(A) Proportions of infection events in the three clusters; (B) proportions of bacterial, fungal, mycoplasma, tuberculosis, and pneumocystis carinii infection events; (C) proportions of single and mixed infection events; (D) proportions of infection site events.