Krebs von den Lungen-6 and surfactant protein-A in interstitial pneumonia with autoimmune features

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Abstract

Interstitial pneumonia with autoimmune features (IPAF) is a special subtype of interstitial lung disease that has received worldwide attention. Krebs von den Lungen-6 (KL-6) and surfactant protein-A (SP-A) can be used as an important biomarker of interstitial lung disease, but its exact relationship with IPAF is poorly understood.

A total of 65 IPAF patients were included in the study and were followed up for 52 weeks. The KL-6 and SP-A were evaluated by chemiluminescence enzyme immunoassay. The above indicators were tested at 2 time points, baseline (the first admission of patients) and 52 weeks. We also collected the indicators of antinuclear antibodies and rheumatoid factor. Based on high-resolution computed tomography evaluations, patients were divided into: aggravation, stable, and improvement group. At same time, 30 age-matched normal people as normal control were recruited, the same information was collected. Correlations among the groups were compared and analyzed.

The KL-6 and SP-A level in IPAF patients were significantly higher than normal controls (fold increase = 11.35 and 1.39, both \( P < .001 \)) and differed significantly at baseline and 52 weeks in IPAF (difference ratio = 37.7% and 21.3%, \( P < .05 \), both). There were significant differences at baseline and 52 weeks \( r \) values of aggravation, improvement, and stable groups for KL-6 were 0.705, 0.770, and 0.344, \( P = .001, .001, \) and .163, and for SP-A the \( r \) value were 0.672, 0.375, and 0.316, \( P = .001, .126, \) and .152. In aggravation group, KL-6 and SP-A were correlated with CT scores (both \( P < .05 \)). Diffusing capacity of the lung for carbon monoxide (DLCO) and forced vital capacity (FVC), % predicted showed a progressive downward trend, with a significant difference at baseline and 52 weeks. Patients with IPAF (difference ratio = 23.8% and 20.6%, both \( P < .05 \)). There was a significant correlation between KL-6 and FVC % predicted and DLCO (both \( P < .05 \)). SP-A negatively correlated with DLCO, but not significantly correlated with FVC % predicted (\( P < .05 \), both).

This study demonstrated that KL-6 and SP-A can reflect disease progression, and both play a key role at reflection of lung epithelial cell injury and fibrosis degree in IPAF.

Abbreviations: ANA = antinuclear antibodies, CTD-ILD = connective tissue disease-interstitial lung disease, DLCO = diffusing capacity of the lung for carbon monoxide, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, HRCT = high-resolution computed tomography.

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1. Introduction

Interstitial pneumonia with autoimmune features (IPAF) is a special subtype of interstitial lung disease (ILD) that was established by the American Thoracic Society and European Respiratory Society ATS/ERS in 2015 and is closely related to connective tissue disease-interstitial lung disease (CTD-ILD).\(^1\)–\(^3\) Both IPAF and CTD-ILD are immune-related ILDs with partially overlapping manifestations in high-resolution computed tomography (HRCT), histopathology, lung dysfunction, etc.\(^{[4]}\) Therefore, the diagnostic and classification criteria for IPAF are also serological and clinical characteristics shared with CTD-ILD.\(^{[5]}\)–\(^{[7]}\) IPAF is diagnosed based on the exclusion of other known immune-related ILDs, and requires at least 2 of 3 clinical, serological, and imaging standards.\(^{[8]}\) The underlying mechanisms and clinical manifestations of IPAF are complex.\(^{[9]}\) The serology of IPAF is also poorly understood, and there is still a lack of consensus in substantive diagnosis.\(^{[10]}\) In addition, the criteria for classification are currently being refined.\(^{[6,8]}\)

HRCT and/or histopathological findings provide direct evidence for the identification of IPAF, and more than 90% of cases are serologically positive for antinuclear antibodies (ANAs) and/or rheumatic factor (RF).\(^{[9]}\) Reduced diffuse function is a manifestation, rather than a feature, of the disease; however, it can still be used as a marker of progression.\(^{[4]}\) Patients with IPAF may have a higher risk of disease progression than patients with CTD-ILD, and follow-up research may shed more light on the disease mechanism.\(^{[9,10]}\)

Krebs von den Lungen-6 (KL-6) is a high molecular weight myxoid glycoprotein that is mainly found on type II alveolar cells and is expressed and secreted by thin bronchial epithelial cells. KL-6 is involved in fibroblast chemotaxis and antiapoptotic effects, can reflect the damage and regeneration of alveolar cells, and is an important biomarker of pulmonary fibrosis.\(^{[11,12]}\) KL-6 is regarded as a core biomarker for the diagnosis of ILD in Japan, as it is closely related to disease activity and can provide prognostic information.\(^{[13]}\)–\(^{[16]}\) Alveolar surfactant proteins (SPs), including A, B, and D subtypes, are the most abundant. SP-A is a representative hydrophilic SP that is involved in the innate immune response, regulates inflammation, and plays a key role in limiting alveolar cavity inflammation as well as for II alveolar cells expressed.\(^{[15,16]}\) KL-6 and SP-A have been extensively studied in CTD-ILD, including dermatomyositis-related ILD, systemic sclerosis-related ILD, and arthritis-related ILD.\(^{[14,17]}\)–\(^{[19]}\)

Although IPAF is currently considered to be an independent disease, many of its associated phenotypes overlap with CTD-ILD, and studies on KL-6 and SP-A in IPAF are lacking.\(^{[20]}\)

In previous studies, we explored the levels of KL-6 and SP-A in IPAF, and found that although they could not be used as specific markers to distinguish between IPAF and CTD-ILD, their levels were higher in patients with these diseases than in normal people and differed significantly between patients with the 2 diseases.\(^{[21]}\) The clinical manifestations of IPAF and other autoimmune diseases are similar and their classifications overlap. As the disease progresses, inconsistencies in lung function, imaging findings, clinical manifestations, and serology may occur; therefore, the application of a single indicator is not rigorous enough for comparative analysis.\(^{[22–25]}\) In this study, we conducted a correlation analysis with multiple clinical indicators to comprehensively explore the value of KL-6 and SP-A in the progression of IPAF.

2. Methods

2.1. Characteristics of study participants

This study included 65 patients with IPAF evaluated at the First Affiliated Hospital of Guangzhou Medical University from October 2016 to October 2018. Diagnosis and classification were based on the IPAF expert consensus established by ERS/ATS in 2015 and were confirmed by imaging and/or pathological and serological evaluations. Patients had to meet the following criteria for inclusion:

1. males and females between 40 and 60 years of age;
2. no surgical history;
3. no metabolic diseases, such as diabetes or hyperthyroidism;
4. no cardiovascular diseases, such as coronary heart disease;
5. no history of cancer;
6. excluded the patients with allergic history of pollen, pet feeding, and fungal or pneumoconiosis patients; and
7. no history of other lung diseases.

General clinical information was collected, lung function was evaluated, and venous blood was collected in the morning on an empty stomach. Seven patients who were ultimately diagnosed with other types of ILD or developed tumors during follow-up were excluded. As a control group, 30 age-matched normal people were recruited, and serum samples were collected from them.

2.2. Blood sample preservation

Five milliliters of fasting venous blood was collected into a procoagulant tube. Then, the sample was centrifuged at 3000 rpm for 30 minutes at room temperature. The supernatant was collected and stored at −80°C until use.

2.3. Serological indicators

KL-6 and SP-A levels in serum were determined by chemiluminescence enzyme immunoassay (Sysmex, Japan). ANAs were detected by indirect immunofluorescence assay with Hep-2 cells as substrate, and the titer of 1:320 as positive defined (INOVA, America). RF was tested by detection Kit (Immunoturbidimetry) (MSKhio, China).

2.4. Pulmonary function tests

Lung function was evaluated using a lung quantifier (Jaeger, Germany), which was operated according to ATS/ERS standards.
Measured indicators included forced expiratory volume in one second (FEV1), forced vital capacity (FVC), FEV1/FVC, total lung capacity (TLC), vital capacity (VC), and dispersion function [(Diffusing capacity of the lung for carbon monoxide (DLCO)].

2.5. High resolution CT
All patients with IPAF underwent chest HRCT, with thin-layer (1-mm) scanning, at 2 time points, at baseline and 1 year later. Since there is no current unified scoring standard for IPAF, the IPAF classification standard published by ATS/ERS in 2015 was used, with reference to the image evaluation methods for ILD in Ying et al.[26] Man et al.[27] Zou et al.[28] and Lee et al.[29] Some of the morphological classification criteria for IPAF are the same as those for CTD-ILD; therefore, we tentatively used part of the CTD-ILD criteria (ground glass shadow, bronchial pull, nodules, and honeycombing in 2 CT sections of the diaphragm and aortic arch). For a more comprehensive assessment, we also combined this with the changes in lesion area and position (affected). Based on these assessments, the IPAF patients were divided into three groups, aggravation, stable, and improvement. All relevant evaluations and scores were conducted by 3 radiologists, 2 respiratory physicians, and 1 rheumatologist at our hospital to provide the most accurate diagnosis and to distinguish ILD from other identifiable diseases.

2.6. Statistical analysis
The data are presented as the mean ± standard deviation, and the variance, t-test, and rank-sum test were used to determine the statistical significance of differences at P < .05. IBM SPSS (Statistics for Windows, Version 22.0; IBM Corp., Chicago, IL, USA), GraphPad Prism 5.0 (GraphPad Software, San Diego, CA), and R statistical package (University of Auckland, New Zealand) were used for data analysis and graphic production.

3. Results
3.1. Characteristics of patients with interstitial pneumonia with autoimmune features (IPAF)
The levels of KL-6 and SP-A in IPAF patients were significantly higher than those in the normal controls (Fold increase = 7.06 and 2.84, Both P < .001). And the lung function index (FEV1% predicted, FVC %predicted, and DLCO) in patient of IPAF were lower than the normal control with significant difference (Difference ratio=17.4%,16.7% and 32.0%, P all < .01). In this study, a higher proportion of IPAF patients were female, but the difference was not statistically significant due to the small sample size (Table 1).

3.2. Trends and correlation analysis of KL-6 and SP-A levels in the aggravation, improvement, and stable groups of IPAF patients
The total KL-6 and SP-A levels in patients with IPAF differed significantly at baseline and 52 weeks (Difference ratio = 37.7% and 21.3%, r = 0.565 and 0.556; P < .05, both). The trends in KL-6 and SP-A levels during the 52-week follow-up are shown in Figure 1. KL-6 and SP-A levels in the aggravation group differed significantly from those in the improvement and stable groups at both baseline and 52 weeks (the r values for KL-6 and SP-A in the aggravation, improvement, and stable groups were 0.705, 0.770, and 0.344, respectively, and 0.672, 0.375, and 0.316, respectively. The P values were .001, .001, and .163, respectively, and .001, .126, and .152, respectively.

| Table 1 | Participants characters. | Normal Control | IPAF | P-value |
|--------|--------------------------|----------------|------|--------|
| N      | 30                       | 65             |      |        |
| Age, years | 54.00 ± 12.61 | 51.00 ± 14.06 | .227 |
| Male/Female, n [%] | 18/12 [150] | 29/36 [81] | .190 |
| BMI, kg/m² | 23.19 ± 3.84 | 24.11 ± 3.65 | .435 |
| WBC, 10⁹/L | 7.30 ± 2.31 | 7.04 ± 2.31 | .399 |
| Neutrophil ratio, % | 68.12 ± 14.08 | 61.70 ± 10.12 | .014 |
| Lymphocyte ratio, % | 23.00 ± 5.20 | 25.50 ± 7.32 | .056 |
| Mononuclear ratio, % | 7.31 ± 2.44 | 8.40 ± 6.33 | .068 |
| Eosinophil ratio, % | 1.32 ± 1.56 | 1.50 ± 1.62 | 1.01 |
| Basophil ratio, % | 0.51 ± 0.21 | 0.40 ± 0.23 | .278 |
| RBC, 10¹²/L | 4.63 ± 0.29 | 4.42 ± 0.56 | .187 |
| Hemoglobin, g/L | 134.00 ± 9.65 | 136.00 ± 14.04 | .543 |
| Thrombocyte, 10⁹/L | 168.00 ± 45.92 | 184.00 ± 60.96 | .245 |
| FEV1, %predicted | 86.70 ± 7.41 | 68.00 ± 13.12 | .001 |
| FVC, %predicted | 82.43 ± 5.39 | 68.40 ± 13.02 | .003 |
| DLCO, % | 91.15 ± 10.44 | 59.90 ± 12.43 | .001 |
| SP-A | 25.80 ± 18.31 | 37.15 ± 39.09 | .001 |
| CRP, mg/L | 0.18 ± 0.53 | 0.26 ± 0.32 | .137 |
| LDH | 177.00 ± 67.90 | 206.00 ± 48.45 | .289 |

BMI=body mass index, CRP=C-reactive protein, DLCO=diffusing capacity of the lung for carbon monoxide, FEV1=forced expiratory volume in 1 second, FVC=forced vital capacity, KL-6=krebs von den Lungen-6, SP-A=surfactant protein-A, WBC=white blood cell.

Figure 1. Trends of KL-6 and SP-A levels in IPAF patients during 52-week follow-up. IPAF=interstitial pneumonia with autoimmune features, KL-6=krebs von den Lungen-6, SP-A=surfactant protein-A. ∗∗∗: P < .001.
3.3. Correlation analysis of HRCT score with KL-6 and SP-A levels in patients with IPAF

The imaging results of patients with IPAF are shown in Table 2. To further analyze the correlation of KL-6 and SP-A levels with HRCT findings in patients with IPAF, we quantified KL-6 and SP-A levels and applied HRCT scores. The results of the analysis showed that KL-6 was significantly correlated with HRCT score ($r = 0.276$, $P < .05$), and SP-A was significantly correlated with HRCT score ($r = 0.246$, $P < .05$; Fig. 2). In the aggravation group of IPAF patients, both SP-A and KL-6 were significantly correlated with HRCT score ($r = -0.276$ and $-0.479$, respectively, $P < .05$ for both). In contrast, no significant correlations were found in the improvement and stable groups.

3.4. Correlation analysis of KL-6 and SP-A levels with lung function

IPAF is a special subtype of ILD that is characterized by interstitial lung damage, and pulmonary ventilation dysfunction often occurs.\cite{10} In this study, DLCO and FVC, % predicted showed a progressive downward trend, with a significant difference between the 2 time points, baseline and 52 weeks (Difference ratio = 23.8% and 20.6%, $r = 0.438$ and 0.513, respectively; $P < .05$ for both). However, after grouping the IPAF patients, we found significant differences between DLCO and FVC, % predicted at baseline and 52 weeks ($r = 0.726$ and 0.641, respectively; $P < .05$), while no significant differences were found in the improvement and stable groups.

Comparison of DLCO and FVC, % predicted with KL-6 and SP-A levels showed that KL-6 was negatively correlated with DLCO and FVC, % predicted ($r = -0.378$ and $-0.345$, respectively; $P < .05$), and SP-A was negatively correlated with DLCO but not with FVC, % predicted ($r = -0.263$ and $-0.091$, respectively; $P < .05$ and 0.47, respectively; Fig. 3). In addition, the correlation of DLCO and FVC, % predicted with age and sex was also analyzed, but no significant correlations or trends were observed.

3.5. Clinical manifestations of patients with IPAF

In this study, Raynaud phenomenon was the most common symptom, which was present in 18.5% of IPAF patients, followed by joint pain/swelling (13.8%), weight loss (12.3%), and morning stiffness (10.8%). Distal digital fissuring and tip ulceration were observed in only 1 case (Table 3).

Table 2
Imaging results.

| Characteristic pulmonary manifestations | IPAF patients, N [%] |
|----------------------------------------|----------------------|
| Reticular pattern                       | 23 [35.4]            |
| Honeycombing                            | 25 [38.5]            |
| Ground glass opacities                  | 38 [55.4]            |
| Nodular lesions                         | 41 [63.1]            |
| UIP                                     | 0                    |
| OP                                      | 3 [4.6]              |
| NSIP and OP                             | 1 [1.5]              |
| UIP                                     | 0                    |
| Traction bronchiectasis or bronchiolectasis | 11 [16.9]          |
| Reduced lung volume                     | 1 [1.5]              |
| Hydropericardium                        | 3 [4.6]              |
| Hydrothorax                             | 7 [10.8]             |
| Pleural thickening                       | 5 [7.7]              |
| Mediastinal lymph node enlargement       | 48 [73.8]            |

LIP = lymphocytic interstitial pneumonia, NSIP = nonspecific interstitial pneumonia, OP = organizing pneumonia, UIP = usual interstitial pneumonia.

Figure 2. Scatter plot of HRCT scores and KL-6 and SP-A levels.
In addition, we referred to the research results of Doishita et al\[^{[31]}\] and Zheng et al\[^{[32]}\] as well as our previous research results\[^{[21]}\]. There was a significant difference in KL-6 levels at baseline and 52 weeks (r = 0.325, P < .05), whereas SP-A levels did not differ significantly between these 2 time points (r = 0.203, P > .05). The differences in KL-6 and SP-A levels at baseline and 52 weeks in the aggravation, improvement, and stable groups were (r = 0.703, 0.473, and 0.638, respectively; P < .05, for all; and r = 0.533, −0.194, and 0.402, respectively; P < .05, = .44, and = .06, respectively). In addition, correlation analyses were performed for KL-6 and SP-A levels and the rates of various signs and symptoms, and for most, no significant correlation was found. However, KL-6 was significantly correlated with Raynaud phenomenon (r = 0.326, P < .05).

### 3.6. Correlation of KL-6 and SP-A with autoimmune factors

The positive rates of autoimmune factor detection in patients with IPAF are summarized in Table 4. No significant positive distribution of specific autoimmune factors was found in the aggravation, improvement, and stable groups. Correlation analysis of KL-6 and SP-A levels with various autoimmune factors yielded no significant correlation.

### 4. Discussion

IPAF is an independent diagnostic classification for ILD with immune characteristics that do not meet the criteria for CTD-ILD\[^{[33,34]}\]. This disease is less common than IPF and CTD-ILD and has a completely different management strategy. Therefore, it should not be ignored in clinical practice\[^{[35,36]}\]. Survival analysis showed that the prognosis of patients with IPAF was worse than that of patients with CTD-ILD. Patients with IPAF were predominantly female and younger than patients with IPF\[^{[37]}\]. Diagnosis and classification of IPAF are based on serological, pulmonary function, imaging, and/or pathological findings. Here, we explored the value of evaluating KL-6 and SP-A levels in patients with IPAF.

HRCT can provide critical evidence for the diagnosis of IPAF, and the higher the degree of honeycombing, the worse the prognosis\[^{[37]}\]. IPAF involves pleural and pulmonary interstitial dysfunction and is mainly manifested by restricted ventilation dysfunction and diffuse dysfunction. FVC, % predicted, and DLCO are the most commonly used indicators of pulmonary function in interstitial pulmonary disease\[^{[9,38]}\]. and we found that FVC, % predicted, and DLCO were significantly decreased in the aggravation group at 52 weeks, when compared to these values at baseline (P < .05) and were negatively correlated with HRCT score. In contrast, FVC, % predicted, and DLCO did not differ significantly between the improvement and stable groups. Liang et al\[^{[39]}\] stated that patients with IPAF suffered from systemic immune dysfunction, leading to pulmonary inflammatory factor infiltration and resulting in lung interstitial, alveolar, and pulmonary vascular damage. Therefore, combined with the imaging findings, we considered that patients with IPAF, under the circumstances of autoimmune disorders, suffered from lung...
interstitial damage, alveolar collapse, bronchial passive tractive dilation, alveolar wall thickening, and airway occlusion, which affected the lung function of the patients. In a longitudinal study of stable immune-associated interstitial pulmonary disease, Sandra et al.[40] demonstrated that the age was lower the better the pulmonary function of female patients. However, this trend was not observed in our patient population. Therefore, we concluded that there may not be sufficient specificity for evaluating lung function in IPAF patients.

In a study of ILD, KL-6 and SP-A were found to be associated with disease progression and are important indicators in the subclasses IPF and CTD-ILD. However, there is not much research on KL-6 and SP-A in IPAF.[41,42] Here, we found that KL-6 and SP-A levels in the aggravation group of IPAF patients showed significant upward trends over time. Based on lung imaging findings and HRCT scores, immune dysfunction and the restructuring and pulmonary interstitial, alveolar, and bronchial injuries were more serious in the aggravation group of IPAF patients than in the improvement and stable groups. Lung tissue injury leads to type II alveolar regeneration and high level expression of KL-6 and SP-A, which enter the circulation and promote lung fibroblast proliferation and migration, resulting in the imaging manifestations of interstitial fibrosis, such as honeycomb lesions and ground glass shadows. In ILD studies by Wang et al.[43] and Behndig et al.,[44] KL-6 and SP-A were confirmed to be closely related to disease activity, that is, the degree of lung injury, and our analysis was consistent with the mechanism inferred from their research.

A correlation analysis of KL-6 and SP-A with lung function may decline more significantly in patients with exacerbation of IPAF and can reflect the degree of disease progression. However, in patients with nonaggravated disease, lung function tests may not have sufficient specificity. Therefore, in patients with IPAF, lung function is not rigorous enough to judge disease progression without judging disease severity. KL-6 and SP-A levels could reflect disease progression in the group of IPAF patients with aggravated disease, but additional studies are needed in groups of patients with stable disease and improvement.

Imaging results were quantified and scored, and a comparative analysis of the values at baseline and at 52 weeks showed that KL-6 and SP-A were positively correlated with the CT scores in the aggravation group. Wang et al.[46] and AI-Salmi et al.[47] proposed that serum KL-6 and SP-A were related to HRCT and could be used as indicators for evaluating the progression of ILD. This is consistent with the findings of this study in patients with IPAF.

Among the patients in this study, Raynaud phenomenon (18.5%) was the most common symptom, and it was significantly correlated with KL-6 levels, whereas distal digital fissuring and tip ulceration were seen in only 1 case each. Gianluca et al hypothesized that this may be because the latter 2 symptoms are highly specific to idiopathic dermatomyositis rather than IPAF.[48] Dysphagia and rash photosensitivity were not observed in this study. The specificity of clinical symptoms in IPAF is low, and some clinical manifestations of CTD-ILD are included in the classification criteria for IPAF; thus, the boundary between the two may not be clear.[49] The symptom specificity in patients with IPAF is low, and the changes in serum KL-6 and SP-A levels are not parallel to the clinical manifestations in the ATS/ERS classification standard.[7]

The detection of serological biological factors, such as the presence of ANA at a high titer of 1:320 or RF at twice the normal value (>60 IU/mL), are important diagnostic and classification criteria for IPAF.[34,49] In this study, 83.1% of IPAF patients showed positive serological manifestations of IPAF, with the highest positive rate for ANA (75.4%), followed by RF (43.1%), although patients were negative for most tested autoantibodies. This is consistent with the results of a CTD-ILD study by Zhang et al.[50] The statistical results of the study by Chartrand et al.

Table 4

| Autoimmune antibodies of patients with IPAF. | IPAF patients, N [%] | P-value (r) | P-value (r) |
|---------------------------------------------|----------------------|-------------|-------------|
| Serological domain                          |                      |             |             |
| ANA≥ 1:320                                  | 54 [63.1]            | 0.259 (0.142)| 0.155 (0.178)|
| RF ≥2× the upper limit of normal            | 40 [75.4]            | 0.152 (0.180)| 0.341 (0.120)|
| Anti-CLP positive                           | 28 [43.1]            | 0.719 (0.046)| 0.704 (0.048)|
| Anti-CCP positive                           | 6 [9.2]              | 0.452 (0.099)| 0.334 (0.122)|
| Anti-dsDNA positive                         | 1 [1.5]              | 0.088 (0.213)| 0.110 (0.200)|
| Anti-Ro (SSA) positive                      | 4 [6.2]              | 0.787 (0.034)| 0.387 (0.109)|
| Anti-La (SSB) positive                      | 1 [1.5]              | 0.088 (0.213)| 0.110 (0.200)|
| Anti-rRNA synthetase positive               | 0.088 (0.213)        | 0.110 (0.200)|
| Anti-topoisomerase (Scl-70) positive         | 3 [4.6]              | 0.734 (0.043)| 0.734 (0.043)|
| Anti-SSA synthetase positive                | 5 [7.7]              | 0.575 (0.071)| 0.305 (0.129)|
| Anti-Jo-1 positive                          | 3 [4.6]              | 0.734 (0.043)| 0.734 (0.043)|
| Anti-KS                                     | 2 [3.1]              | 0.881 (0.019)| 0.140 (0.185)|
| Anti-PM-Scl positive                        | 1 [1.5]              | 0.088 (0.213)| 0.110 (0.200)|
| Anti-MDA-5 positive                         | 0                    | —            | —            |

ANA = antinuclear antibodies, RF = rheumatoid factor.
showed that 91% of patients with IPAF were positive for at least 1 autoantibody, and ANA was the most common. However, according to the results of this study, although a high positive rate of ANA was detected, it did not reflect the progression of IPAF, nor was it significantly correlated with KL-6 or SP-A. Notably, Oldham et al proposed that the survival rate of IPAF patients was significantly lower than that of CTD-ILD patients, and this was not correlated with the rate of ANA positivity. Unfortunately, we did not track survival in this study.

The mechanism underlying the development of autoimmune interstitial lung diseases is not clear at present. At different stages of the disease, that is, aggravation, improvement, and stable, the levels of various autoimmune factors did not change. To date, the correlation between IPAF and autoimmune factors is not clear.

5. Conclusion

Here, to the best of our knowledge, for the first time, we longitudinally evaluated the levels of KL-6 and SP-A, 2 popular markers, in IPAF. Imaging studies showed that the serum markers KL-6 and SP-A are associated with the progression of lung injury in IPAF and can be used to evaluate disease progression in patients with aggravation of IPAF. Therefore, we expect that evaluation of KL-6 and SP-A will help provide new targets for slowing the progression of IPAF and improving patient prognosis. Based on the IPAF classification criteria, we also found that the clinical signs and symptoms were not completely parallel to the changes in imaging, serology, and lung function, and thus lacked sufficient specificity. Therefore, we believe that some of the CTD-ILD symptoms and manifestations currently included in the classification criteria for IPAF need to be improved.

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