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Original Article

The value of KL-6 in the diagnosis and assessment of interstitial lung disease

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Abstract: Objective: To investigate the value of Krebs von den Lungen-6 (KL-6) in the diagnosis and activity assessment of interstitial lung disease (ILD). Methods: The data of 69 ILD patients admitted to our hospital from January 2018 to January 2020 were analyzed retrospectively, and they were included in the ILD group. In addition, 69 patients with connective tissue disease (CTD) admitted to our hospital during the same period were selected and included in the non-ILD (NILD) group. The lung function, pulmonary imaging scores, and KL-6 expression levels were compared between the two groups. The patients in the ILD group were divided into two subgroups: the inactive group and the active group. The pulmonary function, pulmonary imaging scores, and the KL-6 expression levels of the patients in the two subgroups were compared. The value of KL-6 in the diagnosis and the ILD activity evaluation were analyzed. Results: The FEV1, FVC, and DLCO levels in the LID group were lower than they were in the NLID group (P<0.05). The LUS and Warrick scores in the LID group were higher than they were in the NLID group (P<0.05). The FEV1, FVC, and DLCO levels in the active group were lower than they were in the inactive group (P<0.05). The LUS and Warrick scores in the active group were higher than they were in the NLID group (P<0.05). The patients' serum KL-6 levels in the ILD group were higher than they were in the NILD group (P<0.05), and the patients' serum KL-6 levels in the ILD group were higher than they were in the inactive group (P<0.05). The Youden's index of serum KL-6 for the diagnosis of ILD was 421.775 U/ml and the sensitivity and specificity of the serum KL-6 were 91.304% and 95.652%, respectively, showing a high diagnostic value (P<0.05). The Youden's index of the serum KL-6 levels for the evaluation of the ILD activity was den Lungen-6 (KL-, with a sensitivity of 60.976% and a specificity of 100%, showing a moderate evaluation value (P<0.05). Conclusion: KL-6 has a high value in the diagnosis of interstitial lung disease, and a moderate value in the assessment of interstitial lung disease activity.

Keywords: Interstitial lung disease, disease activity, lung function, imaging findings, receiver operating characteristic curve

Introduction

Interstitial lung disease (ILD) is difficult to treat and has a poor prognosis [1, 2]. The timing of Interstitial lung treatment, the choice of the treatment plan, and the degree of disease activity are important for patient prognosis [3, 4]. KL-6 is a high molecular weight glycoprotein with a molecular weight over 1 million. It was first discovered by Japanese scholar Kono Yoo in 1985 [5, 6]. KL-6 belongs to the 9th sequence of lung cell antigens and is widely distributed in the epithelial cells of type II alveoli [7, 8]. The KL-6 levels are abnormally elevated in ILD patients, but elevated KL-6 levels are rarely seen in healthy people or in patients with other lung diseases. The KL-6 level is increased further when the activity of ILD patients enhanced due to an acute attack. Therefore, KL-6 has a high value for the diagnosis and disease assessment of ILD. At present, KL-6 is widely applied in the clinical diagnosis and disease assessment of ILD in Japan. ILD is a diffuse lung disease caused by the loss of function of the alveoli and the bronchioles. It mainly involves the pulmonary interstitium, the alveoli, and the bronchioles. The inducement of ILD is complicated, and CTD-related ILD (CDT-ILD) and idiopathic ILD are commonly diagnosed. There are great differences among ILD with different incentives. In order to clarify the value of KL-6 in clinical diagnosis and disease activity evaluation of ILD with different incentives, this study was carried out in our hospital.

Materials and methods

General data

The data of 69 ILD patients were analyzed retrospectively, and they were included in the ILD group, while 69 CTD patients admitted to our hospital in the same period were included in the non-ILD group. Diagnostic criteria: According to the American College of Rheumatology, the relevant standards for diagnosis were formulated [9]. The diagnosis of ILD is based on the CTD-ILD related diagnostic criteria and the positive detection of anti-amide transport RNA synthetase antibodies [10, 11], and the guidelines for diagnosis and treatment of idiopathic pulmonary interstitial fibrosis jointly formulated by the American Thoracic Society (ATS), the European Respiratory Society (ERS), the Japanese Respiratory Society (JRS), and the Latin American Chest Association (ALAT) [12]. Inclusion criteria: ① Patients who meet the above diagnostic criteria for CTD and ILD; ② The ILD patients with acute exacerbation were included in the ILD activity subgroup, while the CTD patients without any lung diseases or lung injuries were included in the CTD group. ③ Patients who were examined using chest high resolution CT. ④ Patients with complete relevant data in our hospital. Exclusion criteria: ①: ILD patients with occupational exposure, environmental exposure, drug toxicity or other etiologies. ② Patients with tuberculosis, malignant tumors, or other lung diseases or infections. ③ Patients with congenital abnormal lung structures. ④ Patients with bronchial asthma. ⑤ Patients with liver, kidney, heart, brain, or other important organ injuries. ⑥ Patients with acute cardiovascular and cerebrovascular adverse events. ⑦ Patients who underwent surgery in the previous seven days or patients suffering from trauma. ⑧ Patients with incomplete information in our hospital or who were not treated in our hospital after their subsequent transfer. There were 41 males and 28 females in the CTD group (40-75 years old), with an average age of 58.72±8.31 years old. Specific diseases: 22 cases of rheumatoid arthritis, 19 cases of systemic lupus erythematosus, 5 cases of systemic scleroderma, 13 cases of primary Sjogren's syndrome, and 10 cases of dermatomyositis. There were 41 males and 28 females in the CTD group (40-76 years old), with an average of 59.92±8.54 years old. Specific diseases: 6 cases of anti-synthetase syndrome complicated with interstitial lung disease (ASSD ILD), 8 cases of idiopathic pulmonary fibrosis (IPF), 14 cases of idiopathic interstitial pneumonia (IIP), and 41 cases of CDT-ILD. According to the patients' disease activity, the ILD group was divided into an inactive group (28 cases) and an active group (41 cases). Ethical approval was granted by the ethics committee of our hospital.

Methods

Detection of KL-6: 3 ml blood samples were collected from the elbow veins of all the fasting patients. The blood samples were centrifuged for 10 min at a speed of 3000 r/min, and the serum was obtained for examination. The serum KL-6 levels were quantified. The serum was diluted and added into an antibody-binding particle solution containing KL-6 antibody, then they were mixed well, and incubated at 37.5°C for 15 min. Afterwards, the reaction solution was discarded, the serum was washed, and 200 μL alkaline phosphatase labeled antibody was added. The incubation was continued at 37.5°C for 15 min, and the reaction solution was removed. After washing, 200 μl substrate was added and mixed well. The reaction was carried out at 37.5°C for 10 min, and the absorbance of the solution was measured at 475 nm. KL-6 calibration solution was added to the antibody-binding particle solution containing the KL-6 antibodies, and the absorbance was measured using the same method to obtain the KL-6 standard calibration curves. According to the calibration curve, the KL-6 level of each of the diluted serum samples was calculated, and the KL-6 levels of the original serum samples were determined as well.

Pulmonary function: The lung functions of all patients were measured, and their lung function indexes were obtained, including FEV1, DLCO, and FVC.

Lung imaging: All the patients were examined through chest ultrasounds and chest high-definition CT (HRCT) scans. The LUS scoring criteria for lung ultrasound: ① 0 points for normal ventilation. ② 1 point for moderate lung ventilation reduction. ③ 2 points for severe lung ventilation reduction. ④ 3 points for lung parenchymal lesions. Each region was scored with the most serious performance. The sum of the scores of the 12 lung regions was the LUS score, and the scores of both lungs ranged from 0 to 36. HRCT was evaluated by the Warrick score, and the scopes of the bilateral

Table 1. Comparison of the lung function between the LID group and the NLID group ($\bar{x}$±s, %)

Group	n	FEV1	FVC	DLCO
NLID group	69	91.43±4.46	89.62±4.63	86.68±5.33
LID group	69	83.06±7.40	73.07±7.05	63.91±8.04
t		8.050	16.304	19.606
P		<0.001	<0.001	<0.001

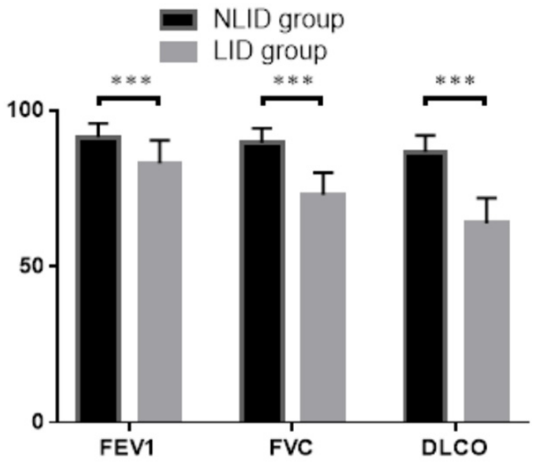

Figure 1. A histogram of the lung function in the LID and NLID groups. *** indicates P<0.001.

Table 2. Comparison of the lung imaging scores between the LID group and the NLID group ($\bar{x}$±s, point)

Group	n	LUS score	Warrick score
NLID group	69	8.31±2.18	6.71±2.37
LID group	69	12.92±3.46	14.47±3.96
t		9.359	13.969
P		<0.001	<0.001

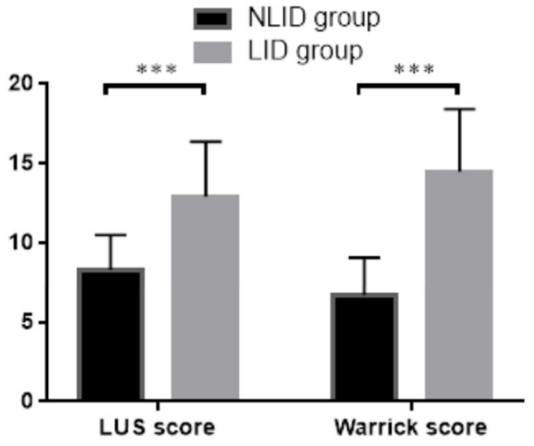

Figure 2. A histogram of the lung imaging scores in the LID and NLID groups. *** indicates P<0.001.

lung lesions and the ground-glass lesions were observed. ① 1 point for ground glass shadows. ② 2 points for irregular pleural margins. ③ 3 points for interlobular septum thickening or pleural downline signs. ④ 4 points for honeycomb shadows. ⑤ 5 points for subpleural cysts. 1 point for 1 to 3 lung segments, 2 points for 4 to 9 lung segments, and 3 points for >9 lung segments, with a total possible score of 30 points.

Research methods

The lung function, the lung imaging scores, and the KL-6 expression levels were compared between the LID group and the NLID group. According to the clinical manifestations and the follow-up treatment, the ILD patients with acute exacerbations and in the active stage were included in the active subgroup, while those without the above manifestations were included in the inactive subgroup. The lung function, the lung imaging scores, and the KL-6 expression levels were compared between the two subgroups. The values, sensitivities, and specificities of KL-6 in the ILD diagnoses and disease activity evaluations were analyzed, and the corresponding optimal diagnostic values (Youden's index) were found according to the formula: sensitivity+specificity-1.

Statistical analyses

SPSS 23.0 was used. The measurement data were tested using *t* tests and expressed as ($\bar{x}$ ±s). The diagnostic and evaluation values were analyzed using AUCs. The classification criteria were: AUC>0.9 means a higher value, 0.7<AUC≤0.9 means a medium value, 0.5≤ AUC≤0.7 means a lower value, and AUC<0.5 means basically worthless.

Results

Comparison of the lung function between the LID group and the NLID group

The FEV1, FVC, and DLCO levels in the LID group were lower than they were in the NLID group (*P*<0.05). See **Table 1** and **Figure 1**.

Comparison of the lung imaging scores between the LID group and the NLID group

The LUS and Warrick scores in the LID group were higher than they were in the NLID group (*P*<0.05). See **Table 2** and **Figure 2**.

Table 3. Comparison of the lung function between the two LID subgroups ($\bar{x}$±s, %)

Group	n	FEV1	FVC	DLCO
Inactive group	28	87.41±5.99	77.64±6.07	68.77±7.32
Active group	41	80.09±6.82	69.95±5.92	60.59±6.77
t		4.594	5.245	4.768
P		<0.001	<0.001	<0.001

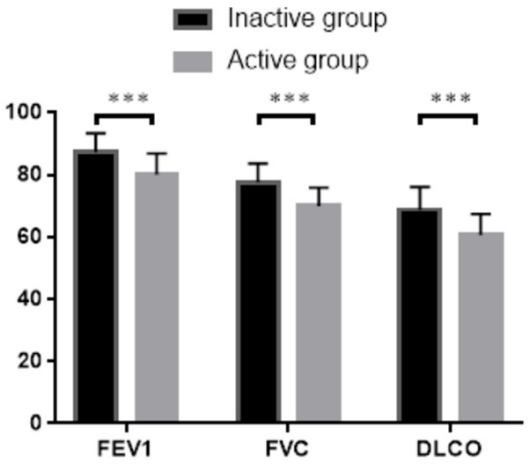

Figure 3. A histogram of the lung function of the two LID subgroups. *** indicates P<0.001.

Table 4. Comparison of the lung imaging scores in the LID subgroups ($\bar{x}$±s, point)

Group	n	LUS score	Warrick score
Inactive group	28	10.78±2.38	11.95±2.71
Active group	41	14.38±3.34	16.19±3.78
t		4.907	5.105
p		<0.001	<0.001

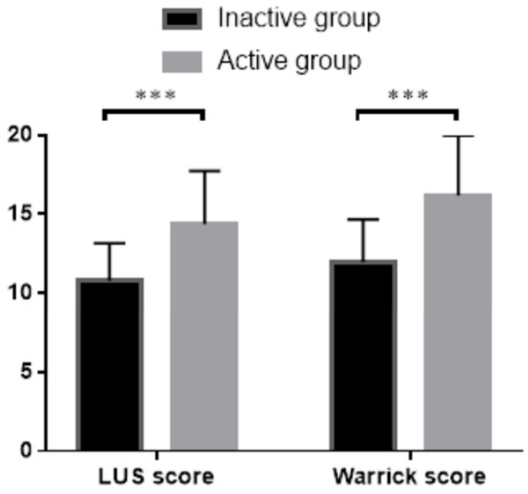

Figure 4. A histogram of the lung imaging scores in the LID subgroups. *** indicates P<0.001.

Comparison of the lung function in the LID subgroup

The FEV1, FVC, and DLCO levels in the active group were lower than they were in the inactive group (*P*<0.05). See **Table 3** and **Figure 3**.

Comparison of the lung imaging scores in the LID subgroup

The patients' LUS and Warrick scores in the active group were higher than they were in the NLID group (*P*<0.05) (**Table 4** and **Figure 4**).

Comparison of the KL-6 expression levels

The KL-6 levels in the ILD group were higher than they were in the NILD group (*P*<0.05), and the KL-6 levels in the active group were higher than they were in the inactive group in the ILD group (*P*<0.05) (**Table 5** and **Figure 5**).

An ROC analysis of KL-6 in ILD diagnosis and disease evaluation

Youden's index of the serum KL-6 level for ILD diagnosis was 421.775 U/ml, and the sensitivity and specificity were 91.304% and 95.652%, respectively, so it has a high diagnostic value (*P*<0.05). Youden's index of the serum KL-6 level for evaluating ILD disease activity was 1268.715 U/ml, and the sensitivity and specificity were 60.976% and 100%, respectively, so it has a moderate evaluation value (*P*<0.05). See **Table 6**. The ROC curve is shown in **Figures 6**, **7**.

Discussion

Patients with ILD may have cough, dyspnea, abnormal gas exchange, limited ventilation disorder characterized by decreased lung volume, hypoxemia, and so on [13, 14]. Respiratory failure can be induced when the disease worsens gradually, resulting in the clinical death of patients. ILD is a common serious complication of CTD, and it can also be induced by other conditions such as anti-synthetase syndrome. There are more than 200 inducements which are characterized by extensive fibrosis and/or inflammation of lung parenchyma [15, 16]. In recent years, the incidence of ILD in China has gradually increased. The proportion of CTD-ILD is relatively high among all kinds of ILD. ILD can

Table 5. Comparison of the patients' serum KL-6 levels ($\bar{x}$±s, U/ml)

Group	n	KL-6	Group	n	KL-6
NILD group	69	226.19±112.57	Inactive group	28	832.62±435.89
ILD group	69	1184.58±573.48	Active group	41	1424.95±533.77
t		13.622	t		4.865
P		<0.001	p		<0.001

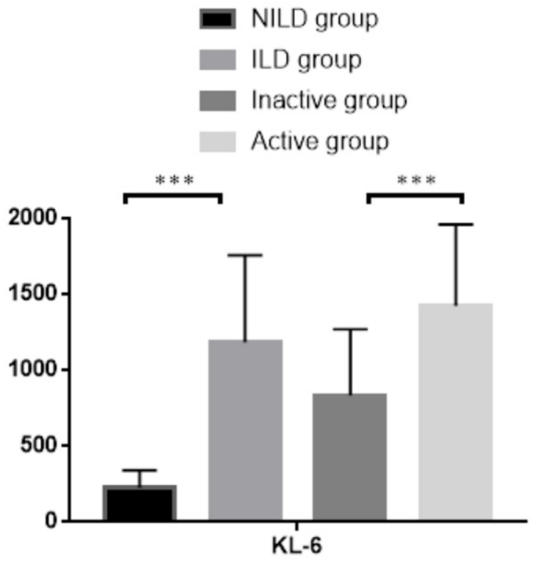

Figure 5. A histogram of the patients' serum KL-6 levels. *** indicates P<0.001.

occur in different stages of the CTD course, and some patients with CTD can even see ILD as their first symptom [17]. Patients with ILD usually have a poor prognosis and high mortality. The activity degree of ILD is closely related to its degree and progress. The higher the activity degree of ILD, the worse the patient's condition and the faster it progresses. Therefore, an early diagnosis and accurate evaluation of ILD activity are of great significance to the formulation of the clinical treatment and to the improvement of the patients' prognoses.

At present, HRCT and bronchoscopy (BAL/TBLB) are the gold standards for ILD diagnosis, especially in the early diagnosis and evaluation of ILD disease activity [18-20]. The diagnosis and condition evaluation are carried out based on pulmonary function, blood gas analysis, surgical lung biopsy, and laboratory index determinations. However, biopsy is an invasive examination, so its application is limited. BAL/TBLB is not easy to carry out. In the early stage of ILD, the performance of some patients under HRCT is atypical and not obvious, and HRCT is easily affected by many factors. Laboratory indicators such as CRP, ESR and WBC are not specific and/or sensitive to the diagnosis of ILD and the assessment of disease activity. Therefore, it is necessary to find a detection index with good sensitivity, specificity, an easy operation and quantitative results. KL-6 has been widely used in Japanese ILD. It is not highly expressed in most patients with other lung diseases, and its expression level is small in healthy people. However, KL-6 is abnormally elevated in most ILD patients, and its expression level increases with an increase in disease activity. This phenomenon provides theoretical support for its application in ILD diagnosis and disease activity assessment.

This study showed that the lung function of ILD patients decreased significantly, the disease activity increased, and the lung function decreased further. Lung imaging showed that the ILD patients developed definite lung injuries. With the increase of disease activity, the scope of the lesion involvement is further expanded, and the severity is gradually aggravated. KL-6 mainly exists on the surfaces of type II alveolar epithelial cells, especially in the tissue sections of idiopathic interstitial pneumonia. The significant proliferation of type II alveolar epithelial cells in ILD patients leads to an increase in the expression of KL-6 on the alveolar surface. Meanwhile, the damage to the alveolar basement membrane leads to an increase in vascular permeability, allowing KL-6 to enter the blood. In this study, the serum KL-6 levels in the ILD group were higher than they were in the NILD group, and the levels in the active group were higher than they were in the inactive group. This suggests that the serum KL-6 levels in ILD patients can be significantly increased, and the serum KL-6 levels are further increased with an increase in disease activity. Our ROC analysis showed that the serum KL-6 level reached 421.775 U/ml or above, which suggests the occurrence of ILD. At this time, the sensitivity and specificity for the ILD diagnosis were 91.304% and 95.652%, respectively, which has a high diagnostic value for ILD diagnoses. When the serum KL-6 level reaches 1268.715 U/ml or above, it indicates

Table 6. The statistical details of the KL-6 levels in our ROC curve analysis of ILD diagnosis and disease evaluation

Item	AUC	Yuden index (U/ml)	Sensitivity (%)	Specificity (%)	Standard error	*P*	95% CI	
							Lower limit	Upper limit
ILD diagnosis	0.933	421.775	91.304	95.652	0.026	0.000	0.882	0.985
Disease assessment	0.796	1268.715	60.976	100.000	0.053	0.000	0.692	0.900

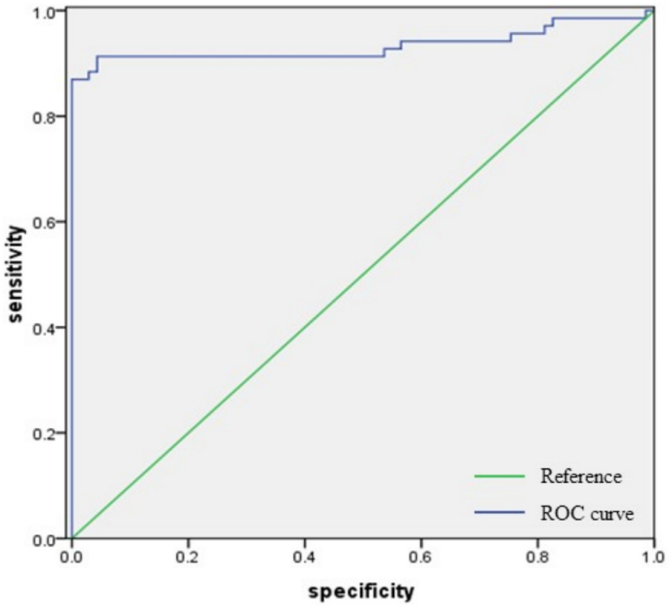

Figure 6. An ROC curve of KL-6 in the diagnosis of ILD.

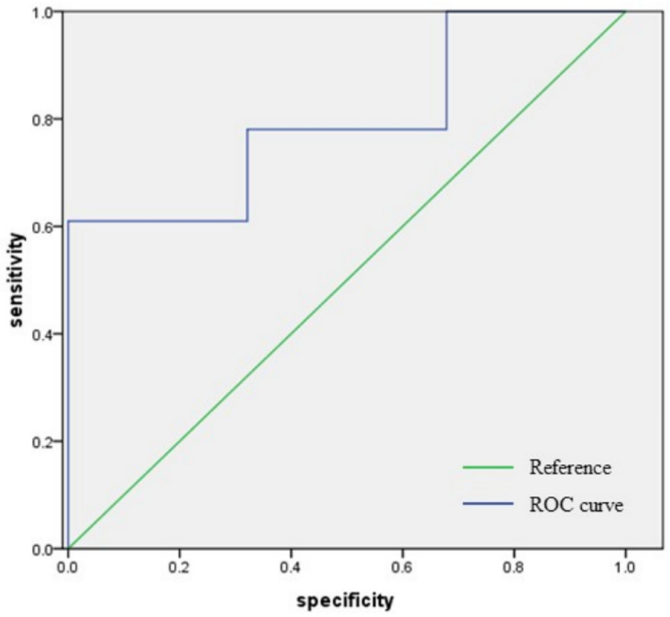

Figure 7. An ROC curve of KL-6 in evaluating ILD disease.

that the patient's ILD disease has entered the active stage. At this time, the sensitivity and specificity for evaluating the activity of ILD disease were 60.976% and 100%, respectively, which has a medium evaluation value. In previous studies on the laboratory indicators of ILD, a comparative analysis of several serologically sensitive markers of ILD KL-6, surfactant proteins (SP-A, SP-D) and monocyte chemoattractant protein-1 (MCP-1) in 33 ILD patients and 82 controls indicated that, the serum KL-6 level was significantly better than other markers, with a cut-off value of 465U/ml, the sensitivity of 93.9% and the specificity of 96.3%, which is basically consistent with the results of this study. The innovation of this study lies in the fact that not only the lung function, pulmonary imaging scores, and KL-6 expression levels of LID and NLID patients were compared, but the differences among the different subgroups of LID were also analyzed, suggesting that KL-6 also has an important application value in predicting the different stages of the disease. In view of the small number of patients included in this study, the correction of the Yoden index needs larger study cohort.

To sum up, KL-6 is of high value for the diagnosis of ILD, and it has a moderate evaluation value for disease activity, but its specificity for disease activity evaluation can be as high as 100%. Therefore, the quantification of the KL-6 levels combined with the patients' clinical manifestations can provide a good reference for the evaluation of ILD disease activity.

Disclosure of conflict of interest

None.

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