International Journal of General Medicine

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Diagnostic Value of Serum KL-6 in Interstitial Lung Diseases

Li Zuo[1,*], Wenhui Zhang[2,*], Ying Wang[3], Xin Qi[1]

[1]Department of Pulmonary and Critical Care Medicine, China Aerospace Science & Industry Corporation 731 Hospital, Beijing, 100074, People's Republic of China; [2]General Practice Clinic, Sijiqing Town Community Health Service Center of Haidian District, Beijing, 100097, People's Republic of China; [3]Department of Pharmacy, Wangtai Branch of Jincheng General Hospital, Jincheng, 048006, People's Republic of China

*These authors contributed equally to this work

Correspondence: Xin Qi, Department of pulmonary and critical care medicine, China Aerospace Science & Industry Corporation 731 Hospital, No. 3, Zhen Gang Nan Li, Feng Tai District, Beijing, 100074, People's Republic of China, Email xinqixq015@163.com

Objective: To explore serum KL-6 level and investigate its diagnostic value in interstitial lung diseases (ILDs).

Methods: Serum KL-6 level was measured using the chemiluminescent enzyme immunoassay. Statistical analysis was performed for determining the KL-6 concentration of each group.

Results: KL-6 level (U/mL) in the ILD group was 1388.321 ±1943.116, which was higher than that in the control group, showing a significant statistical difference. ROC curve analysis based on the receiver operating characteristic curve showed the optimal cut-off value of 402.5U/mL, sensitivity of 77.4%, specificity of 93.4%, and accuracy of 89.4%; through Chi-square test with the two groups, the positive rate of KL-6 in patients with ILD was proved to be significantly higher than that in the control group. KL-6 level was 1063.00±504.757 in the idiopathic pulmonary fibrosis (IPF) group, 1346.892 ±1827.252 in the connective tissue disease-associated interstitial lung disease (CTD-ILD) group, 467.889±288.859 in the organizing pneumonia (OP) group, 8252.333±6050.625 in the pulmonary alveolar proteinosis (PAP) group, and 359.200±392.707 in the sarcoidosis group. The rank sum test showed that the differences were statistically significant. KL-6 level was the lowest in the sarcoidosis group, followed by that in the OP group.

Conclusion: Serum KL-6 level was confirmed to be highly sensitive, specific, and accurate in the diagnosis of ILD. Subgroup analysis showed that the KL-6 level was the lowest in the sarcoidosis group, followed by that in the OP group.

Keywords: ILD, KL-6, diagnostic value, subgroup analysis

Introduction

Interstitial lung diseases (ILDs) are a group of diseases with basic pathological lesions of diffuse pulmonary parenchyma, alveolar inflammation, and interstitial fibrosis, which are featured in exertion dyspnea, diffuse infiltrative shadows on X-ray chest radiographs, restrictive ventilation disorder, reduction of pulmonary carbon monoxide diffusing capacity (DLCO) and hypoxemia. Therefore, ILDs are not a group of independent diseases, but cover more than 200 types of diseases, including idiopathic interstitial pneumonias (IIPs), collagen vascular disease-associated interstitial pneumonia (CTD-ILD), hypersensitivity pneumonia (HP), radiation pneumonitis (RP), drug-induced ILDs (D-ILDs), acute respiratory distress syndrome (ARDS), and sarcoidosis.[1–4] In addition, based on the histological features, IIPs have been further classified into several types, including idiopathic pulmonary fibrosis (IPF), as well as usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP) classified by histopathology. Although each disease has its own clinical features and pathological features, there are also some common clinical features, as well as respiratory pathologic and physiological features, and imaging features. Most types of diseases are long in the course of disease, with gradually deteriorated lung function, which would eventually develop into pulmonary fibrosis or honeycomb lung, thus leading to respiratory failure.

Interstitial lung diseases (ILDs), with extremely complicated etiological factors, are hard to be diagnosed and treated; in addition, they are often misdiagnosed as pneumonia, tuberculosis, or bronchitis, resulting in inappropriate treatment,

Received: 2 January 2024
Accepted: 7 August 2024
Published: 23 August 2024

which would increase the financial burden on patients, delay the treatment, accelerate the deterioration, and even lead to death. Therefore, the diagnosis of ILDs is particularly important. Various interstitial lung diseases, including IIPs, should be diagnosed by high-resolution computed tomography (HRCT), bronchoscopy, and/or surgical lung biopsy (SLB).[4–6] In addition, a series of lung function tests can be used to monitor disease activity and/or predict the prognosis of patients with ILDs.[7] However, these tests should be conducted by specific medical devices, which may cause considerable discomfort to the patients. Therefore, there should be an easy-to-perform, inexpensive, reproducible, and minimally invasive biomarker for diagnosis.

ILD shows common pathophysiological development, ie, the damage or remodeling of type II alveolar parietal cells.[8] Substances derived from type II alveolar epithelial cells have been major potential biomarkers for studying ILD. At present, most widely used biomarker derived from type II alveolar cells is Krebs von den Lungen-6 (KL-6),[9] which was initially discovered by the scholars during the research on lung cancer. In 1985, HE et al conducted a mouse immune test with human lung adenocarcinoma cell lines, and extracted several monoclonal antibodies (VMRC-LCR), of which, anti-KL-6 antibody was the sixth one.[10] KL-6 was found to be mainly localized in the cytoplasm and cell membrane of type II alveolar epithelial cells and bronchial epithelial cells, the cytoplasm partial bronchiolar basal cells and Clara cells, and bronchial glands,[11,12] as well as the epithelial cells in organs such as pancreas, stomach, and breast.[13] Kohno et al[14] tested serum KL-6 levels in different patients, which were found to be higher in patients with lung adenocarcinoma, pancreatic carcinoma, and breast carcinoma as compared with healthy people. Later, it was successively studied that KL-6 was expressed in patients with gastric carcinoma,[13] hepatic cholangiocarcinoma,[15] colorectal carcinoma,[16] and urologic neoplasms,[17] which were found to be associated with TNM staging, suggesting that KL-6 could be taken as an effective biological index for tumor surveillance and prognostic evaluation.[18] Currently, ^{99m}Tc-marked KL-6 antibody has been taken as a tumor-specific radioactive tracer for the diagnosis and treatment of tumors.[19]

As studied, KL-6 could be expressed in damaged and regenerated alveolar epithelial cells.[12] Sakai et al,[20] based on an animal model of lung injury induced by lipopolysaccharide and bleomycin, found elevated KL-6 in serum and BALF/ELF of the patients with ARDS, which could be used to indirectly reflect the extent of damage of alveolar epithelium and disruption of alveolar-capillary barrier.

KL-6, as the glycoprotein with high molecular weight, is now classified as human MUC1 mucin, and regenerated type II alveolar epithelial cells are the main sources of KL-6/MUC1. The survey, initially conducted in Japan, found elevated serum KL-6 level in 70–100% of patients with ILDs, including IIP, CTD-ILD, HP, RP, drug-induced ILD, ARDS, lung sarcoidosis, and pulmonary alveolar proteinosis. These different findings showed that KL-6 could be taken as the serum marker for detecting different interstitial lung diseases (ILDs); therefore, it has been widely used in Japan. In addition, serum KL-6 level has been proven to be able to evaluate disease activity and predict various types of interstitial diseases. Based on these observations, KL-6 is currently the best and most reliable serum marker for the diagnosis of ILDs and determination of the changes in conditions.

However, these results were from studies conducted by Japanese scholars. In this study, it was proposed to analyze the 379 cases admitted in China Aerospace Science & Industry Corporation 731 Hospital and Xinjiekou Community Health Service Center of Xicheng District, from June 1, 2013 to December 31, 2022, so as to explore the value of serum KL-6 levels in the diagnosis of ILDs in Chinese patients and serum KL-6 levels in different populations. The results are hereby reported as follows:

Study Participants and Methods

Inclusion Criteria

ILD Patients

The patients diagnosed with ILD in China Aerospace Science & Industry Corporation 731 Hospital and Xinjiekou Community Health Service Center of Xicheng District from June 1, 2013 to December 31, 2022.

(1) ILD diagnosis: ATS/ERS International Multidisciplinary Consensus Classification of IIPs in 2002:[21] 1) The corresponding medical history, clinical manifestations; 2) Chest imaging shows different forms of interstitial pneumonia; 3) Pulmonary function suggests restrictive ventilation dysfunction and reduced diffusion and/or hypoxaemia; 4)

Bronchoalveolar lavage fluid (BALF) results; 5) Transbronchial lung biopsy (TBLB) or CT-guided lung puncture biopsy or surgical lung biopsy (SLB) pathology.

(2) Diagnosis of IPF based on IPF Evidence-Based Medicine Guidelines released by ATS/ERS/JRS/ALAT in 2011. Brief description: ILD, excluding other causes; HRCT and/or SLB suggest UIP type or possible UIP type.

(3) CTD-ILD: Conforming to ILD and CTD.

Diagnostic criteria for connective tissue diseases[22–27]

Control Group

(1) Community-acquired pneumonia (bacterial pneumonia)

Based on the Diagnosis and Treatment of Community-Acquired Pneumonia (2013)

(2) Chronic obstructive pulmonary disease (COPD)

Based on the Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease (2013, Revised Edition)

(3) Bronchiectasis (BE)

Based on the Expert Consensus on the Diagnosis and Management of Bronchiectasis in Adults (2012)

(4) Tuberculosis

Based on the Code of Practice for Outpatient Treatment of Tuberculosis (2012)

(5) Healthy individuals: Those without abnormal clinical test values during physical examination.

Exclusion Criteria

The participants conforming to any of the following criteria were excluded.

(1) Patients with concomitant malignancy

(2) Patients undergoing haemodialysis

(3) Pregnant women, potentially pregnant women, and lactating women

Data Collection

Basic Clinical Information

Gender, age, blood collection time, and diagnosis

Clinical Features

Symptoms, pulmonary signs

Auxiliary Examinations

Blood routine, biochemical test, rheumatological and immune-related test, blood gas analysis, sputum test, bronchoscopy, etiology test, transbronchial lung biopsy (TBLB), percutaneous lung puncture examination, thoracoscopic lung biopsy, as well as chest radiography.

Measurement of Serum KI-6 Level

About 2–3 mL of venous blood was collected from each patient after hospitalization, and centrifuged for obtaining the serum, which was then frozen in a refrigerator at −30°C, and thawed for testing. KL-6 concentration was measured by chemiluminescent enzyme immunoassay (CLEIA). The salivary liquefied glycochain antigen KL-6 assay kit (chemiluminescence method) provided by FUJIREBIO INC was also used for testing. Serum KL-6 concentration above 402.5 U/mL was considered abnormal.

Statistical Analysis

SPSS19.0 software was used for processing the data. The measurement data were expressed as the mean ± standard deviation. The measurement data were compared by *t* test or non-parametric test, and the counting data were compared by X^2 test. $P<0.05$ indicated that the difference was statistically significant. For KL-6 assay values in the ILD group and control group, the cut-off values were analyzed using the ROC curve. Sensitivity, specificity, and diagnostic accuracy were analyzed.

Study Results

General Data

There were 93 ILD patients, including 50 males and 43 females, with the age of 59.65±12.04 years old. There were 26 patients with IIP, 15 with IPF, 9 with OP, 1 with NSIP, 1 with respiratory bronchiolitis-associated interstitial lung disease (RBILD), 28 with CTD-ILD, 6 with rheumatoid arthritis, 10 with sicca syndrome, 1 with systemic sclerosis, 1 with systemic lupus erythematosus, 1 with dermatomyositis, 3 with angiitis, 1 with anti-Jo-1 antibody syndrome, 1 with undifferentiated connective tissue disease, 4 with unclassified diseases, 5 with sarcoidosis, 1 with HP, 3 with pulmonary alveolar proteinosis, and 2 with lymphangioleiomyomatosis (LAM). There were 286 patients in the control group, including 203 males and 176 females, with the age of 57.51±18.94 years old, including 95 with COPD (74 males and 21 females), with the average age of 58.403 years old; 63 with bronchiectasis (15 males and 48 females), with the average age of 60.292 years old; 78 with pneumonia (50 males and 28 females), with the average age of 59.603 years old; 20 with pulmonary tuberculosis (11 males and 9 females), with the average age of 59.676 years old; and 30 healthy individuals (3 males and 27 females), with the average age of 35.667 years old. There was no difference in gender composition between the ILD group and control group (X^2=0.002, P=0.964>0.05), and there was no difference in age either (t=−1.020, P=0.308>0.05), as shown in Table 1.

Comparison of KL-6 Level Between the ILD Group and the Control Group

KL-6 level (U/mL) in the ILD group was 1357.108±2160.916, and that in the control group was 237.084 ±249.363. *Mann–Whitney U*-test showed that P<0.05, indicating that the difference was statistically significant. KL-6 level in the ILD group was higher than that in the control group.

Distribution of Serum KL-6 Levels in Patients with ILD and Those with Other

Different pulmonary diseases, as well as the healthy individuals, as shown in Figure 1.

KL-6 Level in the ILD Group

KL-6 (U/mL) was 1388.321 ±1943.116 in the ILD group, as shown in Figure 2.

KL-6 Level in the Pneumonia Group

KL-6 (U/mL) was 234.744±331.324 in the pneumonia group, as shown in Figure 3.

KL-6 Level in the Pulmonary Tuberculosis Group

KL-6 (U/mL) was 305.500±341.404 in the pulmonary tuberculosis group, as shown in Figure 4.

KL-6 Level in the COPD Group

KL-6 (U/mL) was 224.916±100.928 in the COPD group, as shown in Figure 5.

KL-6 Level in the Bronchiectasis Group

KL-6 (U/mL) was 266.492±303.855 in the bronchiectasis group, as shown in Figure 6.

Table 1 Basic Patient Information

Type of Disease		Number of Cases	Gender		Average Age
			Male	Female	
ILD group		93	50	43	58.078
	COPD	95	74	21	58.403
	Pneumonia	78	50	28	59.603
Control group	Pulmonary tuberculosis	20	11	9	59.676
	Bronchiectasis	63	15	48	60.292
	Healthy population	30	3	27	35.667
Total		379	203	176	55.288

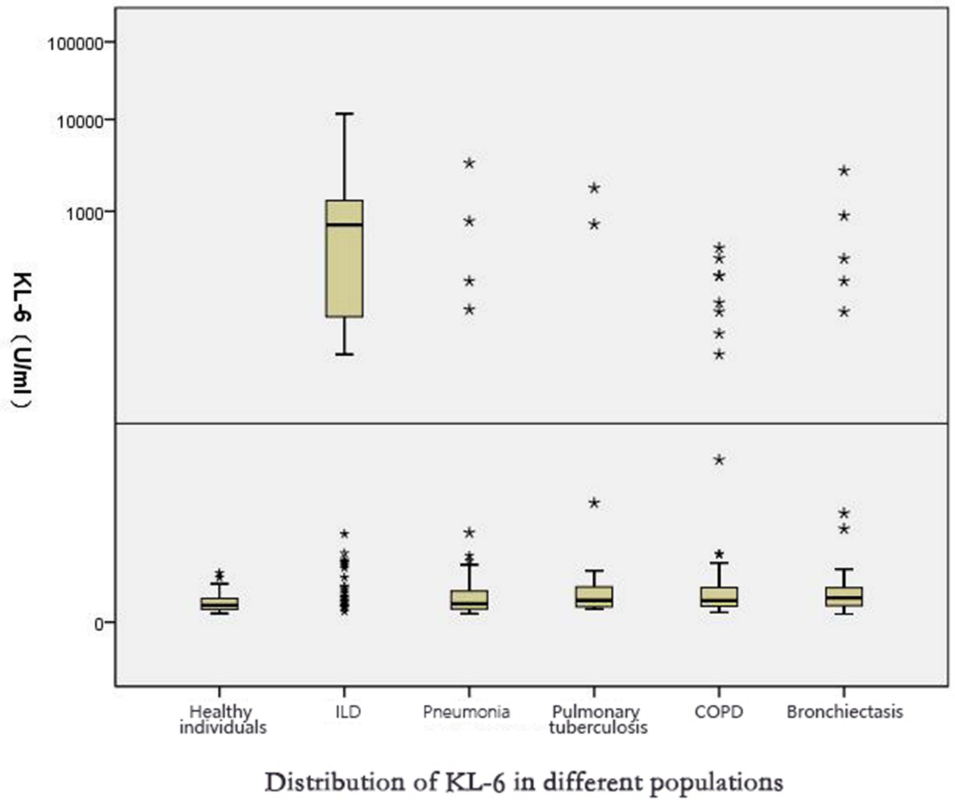

Figure 1 KL-6 level in patients with ILD was significantly higher than that in patients with other pulmonary diseases and healthy individuals.

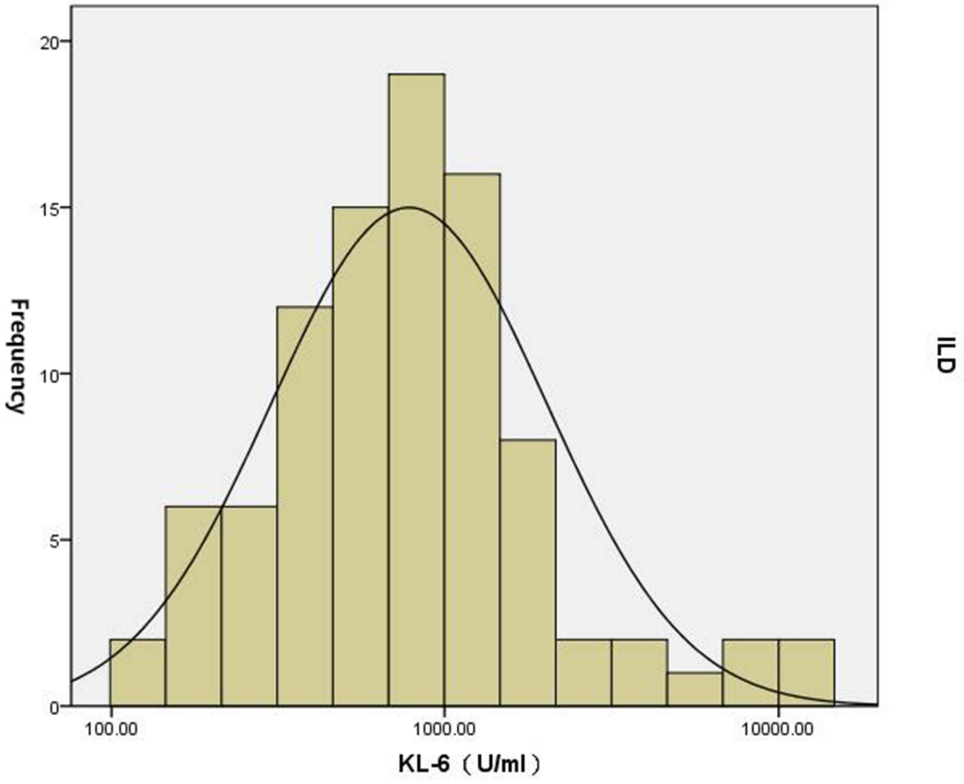

Figure 2 KL-6 level in the ILD group.

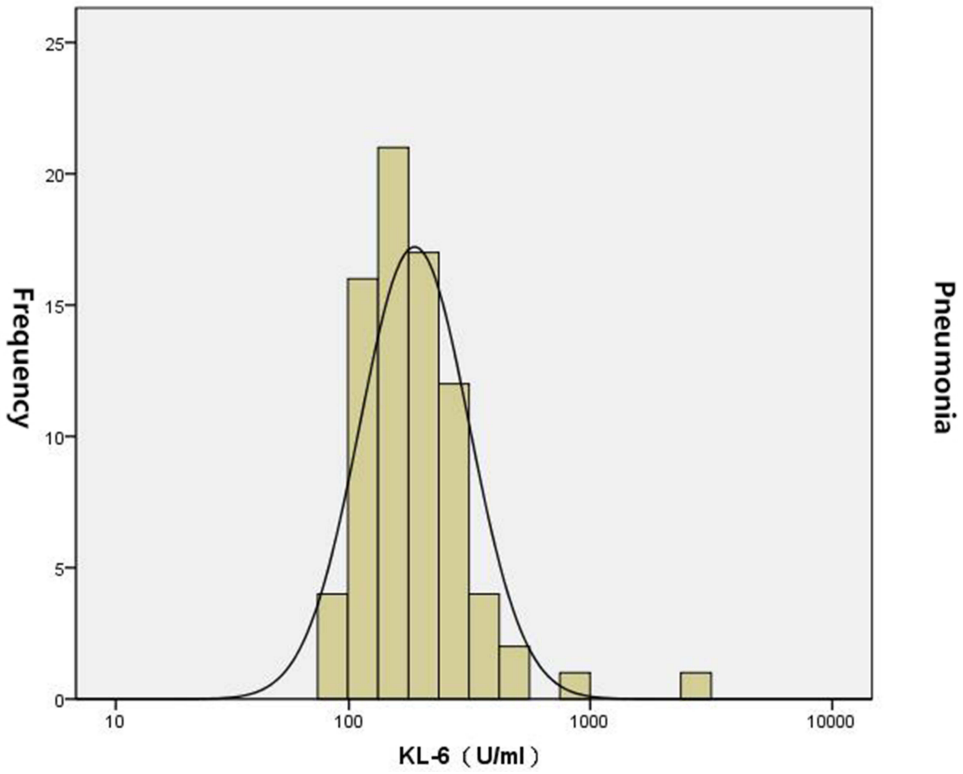

Figure 3 KL-6 level in the pneumonia group.

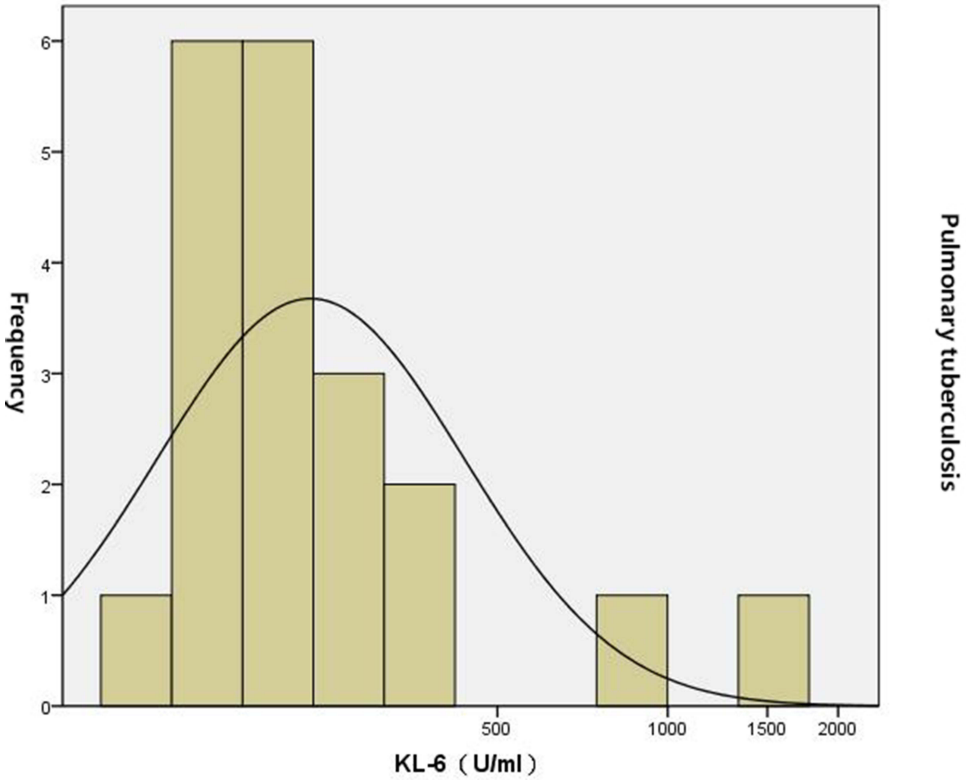

Figure 4 KL-6 level in the pulmonary tuberculosis group.

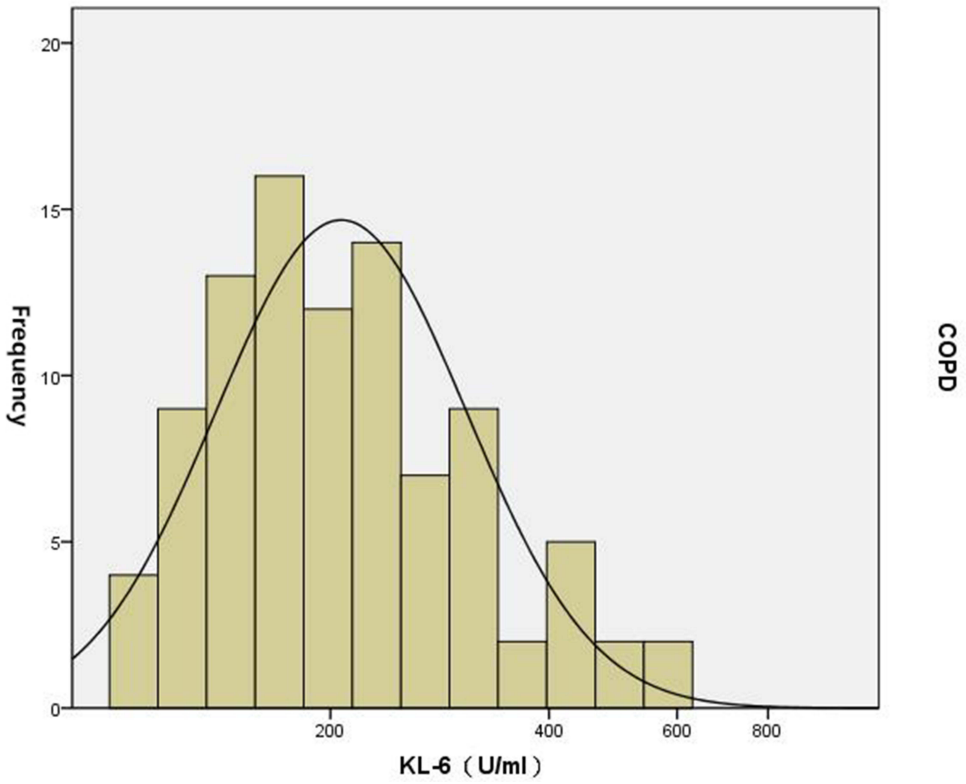

Figure 5 KL-6 level in the COPD group.

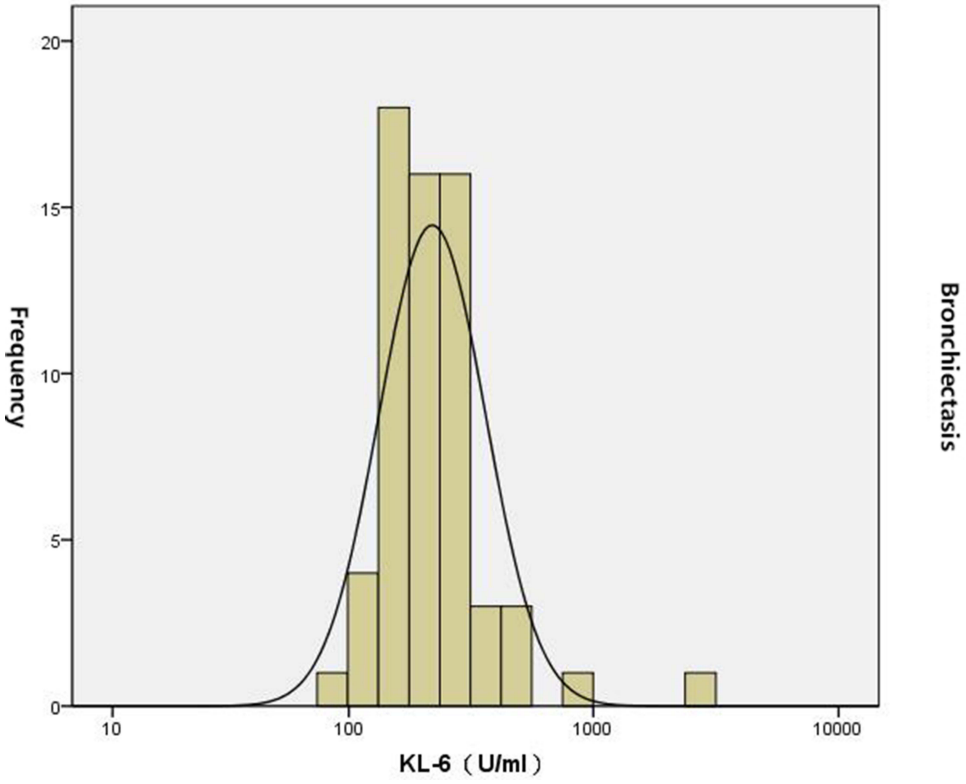

Figure 6 KL-6 level in the bronchiectasis group.

KL-6 Level in the Healthy Group

KL-6 (U/mL) was 174.333±56.305 in the healthy group, as shown in Figure 7.

Comparison of KL-6 Levels Between Different ILD Subgroups

KL-6 (U/mL) was 1063.00±504.757 in the IPF group, 1346.892 ±1827.252 in the CTD-ILD group, 467.889±288.859 in the OP group, 8252.333±6050.625 in the PAP group, 359.200±392.707 in the sarcoidosis group, 437 and 414 in two LAM patients, 680 in one NSIP patient, 330 in one RBILD patient, and 1046 in one HP patient. Kruskal–Wallis test showed that P=0.003<0.05 in the IPF group, CTD-ILD group, OP group, PAP group, and sarcoidosis group, indicating that the difference was statistically significant. Mann–Whitney *U*-test showed that P<0.05 in the IPF group and CTD-ILD group, indicating that the difference was statistically significant. KL-6 level was the lowest in the sarcoidosis group, followed by that in the OP group, as shown in Figure 8.

Sensitivity and Specificity of KL-6 Test

ROC curve analysis based on the receiver operating characteristic curve showed that the cut-off value was 402.5U/mL, the sensitivity was 77.4%, the specificity was 93.4%, and the accuracy was 89.4%. In the ILD group, there were 72 positive cases and 21 negative cases, while in the control group, there were 19 positive cases and 267 negative cases. Based on the chi-square test, X^2 =192.675, P<0.05, indicating that the difference was statistically significant, as shown in Figure 9 and Table 2:

Discussion

Interstitial lung diseases (ILDs), with complicated etiological factors, are hard to be diagnosed and treated, and their misdiagnosis and mistreatment would delay the treatment, accelerate the deterioration, and even lead to death. HRCT, bronchoscopy, and/or SLB are basic steps for confirming various ILDs. However, for some patients with acute and aggravated interstitial pneumonia, the above tests may be dangerous and may even aggravate the conditions; some

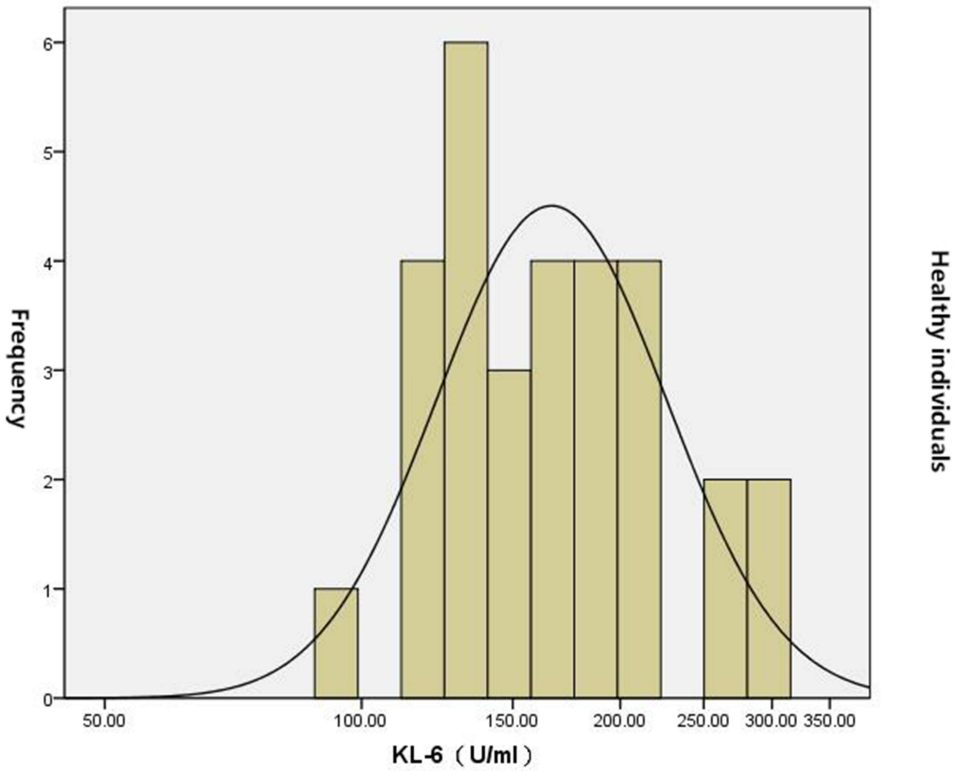

Figure 7 KL-6 level in the healthy group.

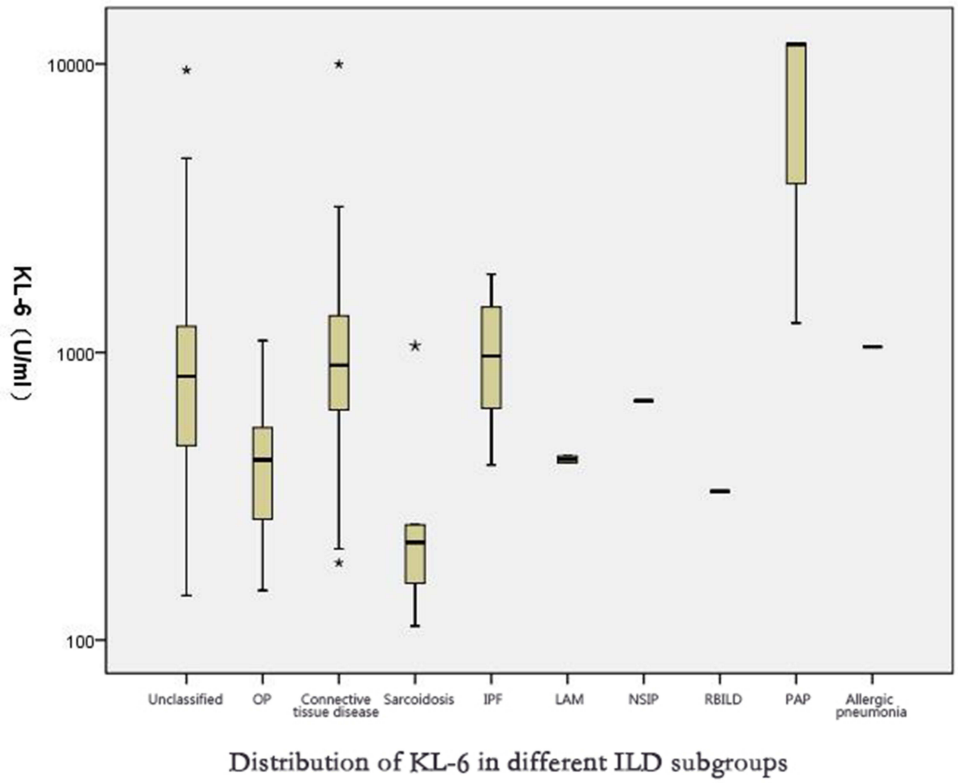

Figure 8 Comparison of KL-6 levels between different ILD subgroups.

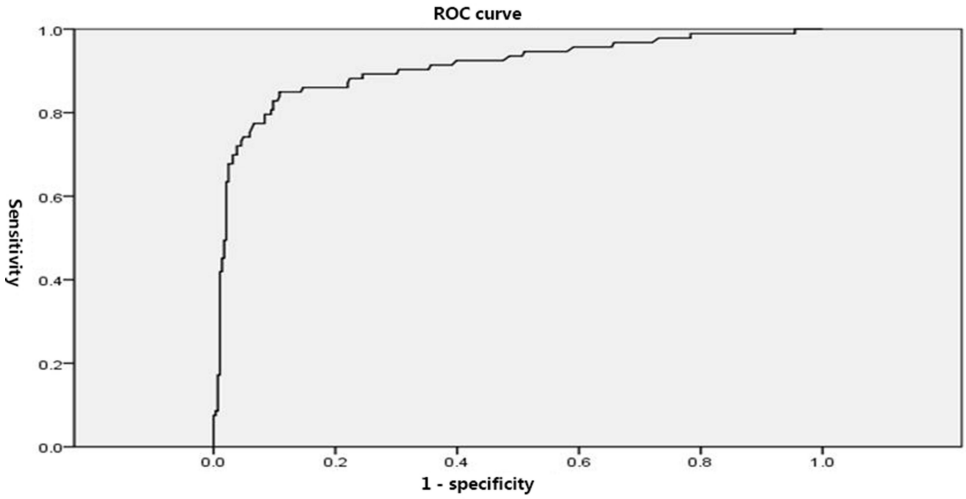

Figure 9 The area under ROC curve was 0.909, indicating the high diagnostic value of KL-6.

patients could not tolerate or have no conditions to undergo the above tests. Clinical symptoms, X-ray chest film, HRCT, pulmonary function test, bronchoalveolar lavage, and lung biopsy are important tools for evaluating the conditions of interstitial lung diseases (ILDs). However, in the case of pulmonary infections, the changes in the above indicators resemble the performance of ILD; therefore, they are of little significance in distinguishing disease activity and concurrent infections. Although HRCT has a certain differential diagnostic significance, its specificity is not ideal. Although lung biopsy and BALF are highly specific, they should be performed with certain medical devices and

Table 2 Four-Fold Table of KL-6 Tests and Clinical Criteria

	Clinical Criteria		Total
	ILD Group	Control Group	
KL-6 results			
Positive	72	19	91
Negative	21	267	288
Total	93	286	379

operating level, and they may cause considerable discomfort; in addition, they are invasive tests, which are low in repeatability and limited in clinical application.

An easy-to-perform, minimally invasive, and reproducible biomarker should be taken as an ideal diagnostic method. Foreign researchers showed that surfactant protein A (SP-A) and surfactant protein D (SP-D) could be taken as the detectable serum markers.

Later, they paid attention to another serum marker - KL-6. KL-6 was initially taken as a serum tumor biomarker for lung carcinoma, breast carcinoma, and pancreatic carcinoma. However, in view of the high rate of false positive cases in pulmonary fibrosis patients, the diagnostic accuracy rate of KL-6, as a tumor marker, was inferior to that of carcino-embryonic antigen (CEA).[14] A further study identified the potential of KL-6 as a biomarker of ILDs, because the benign ILDs did not show significantly elevated serum KL-6 level.[28] The collaborative study on KL-6 was first conducted by the Diagnostics Division of Eidia (Tokyo, Japan) in 1992. In 1996, the clinical practicability of KL-6 was reconfirmed in clinical studies conducted by 14 research centers. The results of this study promoted the development of the enzyme linked immunosorbent assay (ELISA), and a large number of samples were collected for teasing KL-6. In 1999, the health insurance in Japan took KL-6 as a diagnostic marker for ILDs, and then over 2 million KL-6 samples would be tested in Japan each year.

KL-6 was found to be mainly expressed in Type II alveolar epithelial cells, respiratory bronchiolar epithelial cells, and bronchial gland epithelial cells. Type I alveolar cells, goblet cells, and mucus cells of bronchial glands would not express KL-6. Ohnishi et al[29] identified KL-6 as the best indicator for the diagnosis of ILDs, which was significantly superior to SP-A and SP-D, and its change could also be taken as an efficacy evaluation index for ILDs. In contrast to indicators such as SP-A and SP-D, in addition to ILDs, no elevated serum KL-6 level was found in bacterial pneumonia, emphysema and bronchiectasis, and pulmonary tuberculosis. There may be two reasons: 1. The high level of KL-6 in serum may be associated with the increased permeability of Type II alveolar epithelial cells and/or glandular epithelial cell membrane of the bronchus, and/or disruption of the qi-blood barrier in the lung; 2. The molecular weight of SP-A and SP-D was lower than that of KL-6, which would result in high levels of SP-A and SP-D in serum of the patients with various lung diseases.

The first report regarding the serum KL-6 level showed the positive rate of KL-6 in each group (cut-off value: 520U/mL), ie, 11% in bronchial asthma group, 40% in emphysema group, 40% in bronchiectasis group, 43% in pulmonary tuberculosis group, and 58% in interstitial pneumonia group (significantly higher than the first four groups); in this study, the mean KL-6 level in healthy individuals was 258±131U/mL, which was significantly lower than that in the interstitial lung disease (ILD) group.[14] Ohnishi et al[29] studied 33 ILD patients (21 with IPF and 12 with CTD-ILD) and 82 control participants (70 healthy individuals and 12 patients with bacterial pneumonia), and compared the serum KL-6 levels; ROC curve showed that KL-6 can be taken as a diagnostic marker of ILDs. A growing number of studies showed that multiple ILDs such as RP, HP, and drug-induced pneumonia had elevated KL-6 expression.[30–32] Another study showed that serum KL-6 level was significantly elevated in the clinical activity period of PAP, which can be used to evaluate the severity of disease.[33] This study showed that serum KL-6 level in the ILD group was significantly higher than that in the pneumonia group, pulmonary tuberculosis group, COPD group, bronchiectasis group, and the healthy group, which was consistent with the previous studies.

One study found that KL-6 levels in patients with IPF and CTD-ILD were abnormally elevated, and the KL-6 level in 93.9% of the ILD patients was higher than the cut-off value - 465U/mL.[29] Another study suggested elevated serum KL-6 levels in patients with rheumatoid arthritis, sicca syndrome, systemic sclerosis, polymyositis/dermatitis, and CTD-ILD.[34,35] Satosh et al[36] measured serum KL-6 levels in 240 patients with connective tissue diseases; in 67 patients with CTD-ILD, KL-6 level was abnormally elevated; the value above 500 U/mL suggested the presence of ILD, while the value above 1000 U/mL suggested the presence of CTD-ILD. Okada et al[37] studied 20 patients with COP; they took 500U/mL as the cut-off value; and the results showed that 17 patients had elevated levels (502–3500 U/mL, with an average of 1206.3 U/mL), and 3 patients had normal levels (104–460 U/mL, with an average of 282.1 U/mL). Bonella et al[38] found that the average level of KL-6 in patients with PAP was 2049±1893 U/mL. Kitaichi et al[39] found that the average level of KL-6 in 36 patients with sarcoidosis was 449.3±66.3U/mL, which was lower than the cut-off value. In this study, subgroup analysis was conducted on the IPF group, CTD-ILD group, OP group, PAP group, and sarcoidosis group, and found that KL-6 (U/mL) was 1063.00 ±504.757 in the IPF group, 1346.892±1827.252 in the CTD-ILD group, 467.889±288.859 in the OP group, 8252.333 ±6050.625 in the PAP group, and 359.200±392.707 in the sarcoidosis group. Kruskal–Wallis test showed that $P<0.05$, indicating that the difference was statistically significant; KL-6 level was the lowest in the sarcoidosis group (below the cut-off value), followed by the OP group. The results of this study were consistent with the results of above studies.

Ohnishi et al[29] compared the serum KL-6 levels between 33 patients with ILDs (21 with IPF and 12 with CTD-ILD) and 82 control participants (70 healthy individuals and 12 patients with bacterial pneumonia), and obtained a cut-off value of 465U/mL; the sensitivity, specificity, and accuracy were 93.9%, 96.3%, and 95.7%, respectively. Satosh et al[36] took the cut-off value of KL-6 level as 500U/mL. The cut-off value calculated in this study was 402U/mL, with the sensitivity of 77.4%, specificity of 93.4%, and accuracy of 89.4%. Considering the association with racial difference, types, and distribution of diseases, previous studies were mainly conducted by Japanese, European, and American researchers on non-native people with fewer types of diseases.

In this study, there were fewer ILD cases, and the situation was the same in each subgroup; therefore, the sample size should be increased for further validation and research. In addition, this study, as a cross-sectional study, should be further followed up, and the relationship between KL-6 and ILD activity, efficacy, and prognosis should be observed.

Conclusion

KL-6, as an easy-to-perform, inexpensive, reproducible, and minimally invasive biomarker, is of great significance to the diagnosis of ILDs. Serum KL-6 level can be used to diagnose ILDs, with high sensitivity, specificity, and accuracy. The subgroup analysis on ILDs showed that KL-6 level was the lowest in the sarcoidosis group, followed by the mechanical pneumonia group.

Statement of Ethics

This study was approved by the ethics committee of the China Aerospace Science & Industry Corporation 731 Hospital. We certify that the study was performed in accordance with the 1964 declaration of HELSINKI and later amendments. Informed consent was waived by the Ethics Committee of China Aerospace Science & Industry Corporation 731 Hospital. Due to the nature of this study and the temporary inability to contact patients in a timely manner to obtain consent, the ethics Committee of China Aerospace Science & Industry Corporation 731 Hospital granted patient consent to waive review of medical records. The decision was made in accordance with ethical guidelines that prioritize protecting patient privacy and advancing medical knowledge. To ensure the confidentiality of patient data, all personally identifiable information has been removed from the records, and the data is analyzed anonymously.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Funding

There is no funding to report.

Disclosure

The authors have no conflicts of interest to declare for this work.

References

1. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). *Am J Respir Crit Care Med*. 2000;161(2):646–664. doi:10.1164/ajrccm.161.2.ats3-00
2. American Thoracic Society. European Respiratory Society. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. *Am J Respir Crit Care Med*. 2002;165(2):277–304. doi:10.1164/ajrccm.165.2.ats01
3. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med*. 2011;183(6):788–824. doi:10.1164/rccm.2009-040GL
4. Kinnula VL, Ishikawa N, Bergmann U, Ohlmeier S. Proteomic approaches for studying human parenchymal lung diseases. *Expert Rev Proteomics*. 2009;6(6):619–629. doi:10.1586/epr.09.80
5. King TE. Clinical advances in the diagnosis and therapy of the interstitial lung diseases. *Am J Respir Crit Care Med*. 2005;172(3):268–279. doi:10.1164/rccm.200503-483OE
6. Kim R, Meyer KC. Therapies for interstitial lung disease: past, present and future. *Ther Adv Respir Dis*. 2008;2(5):319–338. doi:10.1177/1753465808096948
7. British Thoracic Society recommendation. The diagnosis, assessment and treatment of diffuse parenchymal lung disease in adults. *Thorax*. 1999;54 (Suppl 1):S1–14. doi:10.1136/thx.54.suppl_1.S1
8. Nukiwa T. The role of biomarkers in management of interstitial lung disease: implication of biomarkers derived from type II pneumocytes. In: Du Bois RM, Richeldi L, editors. *The European Respiratory Monograph 46 Interstitial Lung Disease*. Leeds: Maney Publishing; 2009:47–66.
9. Ishikawa N, Hattori N, Yokoyama A, Kohno N. Utility of KL-6 in the clinical management of interstitial lung diseases. *Respir Investig*. 2012;50 (1):3–13. doi:10.1016/j.resinv.2012.02.001
10. Kawano. ヒト肺癌に対するモノクロ-ナル抗体の作製と臨床診断への応用に関する研究 [Monoclonal Antibodies to Human Pulmonary Carcinoma and Their Application to Clinical Diagnosis]. Journal of Medicine, Hiroshima University. 1985;33(6):971. Japanese.
11. Hinata N, Takemura T, Ikushima S, et al. Phenotype of regenerative epithelium in idiopathic interstitial pneumonias. *J Med Dent Sci*. 2003;50 (3):213–224.
12. Ohtsuki Y, Fujita J, Hachisuka Y, et al. Immunohistochemical and immunoelectron microscopic studies of the localization of KL-6 and epithelial membrane antigen (EMA) in presumably normal pulmonary tissue and in interstitial pneumonia. *Med Mol Morph01*. 2007;40(4):198–202. doi:10.1007/s00795-007-0382-7
13. Inagaki Y, Tang W, Xu H, et al. Sustained aberrant localization of KL-6 mucin and beta- catenin at the invasion front of human gastric cancer cells. *Anticancer Res*. 2011;31(2):535–542.
14. Kohno N, Aldyama M, Kyoizumi S, Hakoda M, Kobuke K, Yamakido M. Detection of soluble tumor- associated antigens in sera and effusions using novel monoclonal antibodies, KL-3 and KL-6, against lung adenocarcinoma. *Jpn1Clin On-Col*. 1988;18(3):203–216.
15. Zhang W, Tang W, Lnagaki Y, et al. Positive KL- 6 mucin expression combined with decreased membranous beta- catenin expression indicates worse prognosis in colorectal carcinoma. *Oncol Rep*. 2008;20(5):1013–1019.
16. Xu HL, Inagaki Y, Seyama Y, et al. Expression of KL-6 mucin, a human MUCl mucin, in intrahepatic cholangiocarcinoma and its potential involvement in tumor cell adhesion and invasion. *LifeSci*. 2009;85(9–10):395–400. doi:10.1016/j.lfs.2009.07.004
17. Fukushima M, Higuchi K, Shimojo H, Uehara T, Ota H. Distinct cytoplasmic expression of kl-6 mucin in chromophobe renal cell carcinoma: a comparative immunohistochemical study with other renal epithelial cell tumors. *Acta Histochem Cytochem*. 2012;45(5):301–308. doi:10.1267/ahc.12020
18. Tang W, Inagaki Y, Kokudo N, et al. KL-6 mucin expression in carcinoma of the ampulla of Vater: association with cancer progression. *World J Gastroenterol*. 2005;11(35):5450–5454. doi:10.3748/wjg.v11.i35.5450
19. Matsumura K, Niki I, Tian H, et al. Radioimmunoscintigraphy of pancreatic cancer in tumor- bearing athymic nude mice using (99m) technetium-labeled anti-KL-6/MUCI antibody. *Radiat Med*. 2008;26(3):133–139. doi:10.1007/s11604-007-0207-6
20. Sakai M, Kubota T, Ohnishi H, Yokoyama A. A novel lung injury animal model using KL-6 measurable human MUCl expressing mice. *Biochem Biophys Res Commun*. 2013;432(3):460–465. doi:10.1016/j.bbrc.2013.01.123
21. ATS/ERS International Multidisciplinary Consensus Classification of IIPs; 2002.
22. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum*. 1988;31(3):315–324. doi:10.1002/art.1780310302
23. Bohan A, Peter JB. Polymyositis and dermatomyositis. *N Engl J Med*. 1975;292(7):344–347. doi:10.1056/NEJM197502132920706
24. Masi AT; Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). *Arthritis Rheum*. 1980;23(5):581–590. doi:10.1002/art.1780230510
25. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum*. 1997;40(9):17–25. doi:10.1002/art.1780400928
26. Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjo¨gren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis*. 2002;61(6):554–558. doi:10.1136/ard.61.6.554
27. Kasukawa R, Tojo T, Miyawaki S. Preliminary diagnostic criteria for classification of mixed connective tissue disease. In: Kasukawa R, Sharp GC, editors. *Mixed Connective Tissue Disease and Anti-Nuclear Antibodies*. Amsterdam: Elsevier; 1987:41–47.

28. Kohno N, Kyoizumi S, Awaya Y, Fukuhara H, Yamakido M, Akiyama M. New serum indicator of interstitial pneumonitis activity. Sialylated carbohydrate antigen KL-6. *Chest*. 1989;96(1):68–73. doi:10.1378/chest.96.1.68
29. Ohnishi H, Yokoyama A, Kondo K, et al. Comparative study of KL-6, surfactant protein-A, surfactant protein-D, and monocyte chemoattractant protein-1 as serum markers for interstitial lung diseases. *Am J Respir Crit Care Med*. 2002;165(3):378–381. doi:10.1164/ajrccm.165.3.2107134
30. Ohnishi T, Yamada G, Tanaka H, et al. A case of chronic hypersensitivity pneumonia with elevation of serum SP-D and KL-6. *Nihon Kokyuki Gakkai Zasshi*. 2002;40(1):66–70.
31. Goto K, Kodama T, Sekine I, et al. Serum levels of KL-6 are useful biomarkers for severe radiation pneumonitis. *Lung Cancer*. 2001;34 (1):141–148. doi:10.1016/S0169-5002(01)00215-X
32. Ohnishi H, Yokoyama A, Yasuhara Y, et al. Circulating KL-6 levels in patients with drug induced pneumonitis. *Thorax*. 2003;58(10):872–875. doi:10.1136/thorax.58.10.872
33. Lin FC, Chen YC, Chang SC. Clinical Importance of Bronchoalveolar Lavage Fluid and Blood Cytokines, Surfactant Protein D, and Kerbs von Lungren 6 Antigen in Idiopathic Pulmonary Alveolar Proteinosis. *Ma Yo Clin Proc*. 2008;83(12):1344–1349. doi:10.4065/83.12.1344
34. Fukaya S, Oshima H, Kato K, et al. KL-6 as a novel marker for activities of interstitial pneumonia in connective tissue diseases. *Rheumatol Int*. 2000;19(6):223–225. doi:10.1007/s002960000064
35. Ogawa N, Shimoyama K, Kawabata H, Masaki Y, Wano Y, Sugai S. Clinical significance of serum KL-6 and SP-D for the diagnosis and treatment of interstitial lung disease in patients with diffuse connective tissue disorders. *Ryūmachi*. 2003;43(1):19–28.
36. Doishita S, Inokuma S, Asashima H, et al. Serum KL-6 level as an indicator of active or inactive interstitial pneumonitis associated with connective tissue diseases. *Intern Med*. 2011;50(23):2889–2892. doi:10.2169/internalmedicine.50.5866
37. Okada F, Ando Y, Honda K, Tanoue S, Matsumoto S, Mori H. Comparison of pulmonary CT findings and serum KL-6 levels in patients with cryptogenic organizing pneumonia. *Br J Radiol*. 2009;82(975):212–218. doi:10.1259/bjr/72775434
38. Bonella F, Ohshimo S, Miaotian C, Griese M, Guzman J, Costabel U. Serum KL-6 is a predictor of outcome in pulmonary alveolar proteinosis. *Orphanet J Rare Dis*. 2013;8(1):53. doi:10.1186/1750-1172-8-53
39. Kitaichi N, Ariga T, Kase S, Yoshida K, Namba K, Ohno S. Usefulness of quantifying serum KL-6 levels in the follow-up of uveitic patients with sarcoidosis. *Graefes Arch Clin Exp Ophthalmol*. 2006;244(4):433–437. doi:10.1007/s00417-005-0081-9