

KL-6 in Lung Diseases

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Interstitial lung diseases (ILDs) represent a large, heterogeneous group of more than 200 different entities, most of which are classified as rare diseases. Accurate diagnosis of Idiopathic Pulmonary Fibrosis (IPF) is critical, as other forms of ILD that have similar clinical presentations to IPF require different treatment strategies. Imaging plays an essential role in the diagnosis of ILDs. Several scientific authors deal with the idea of combining IPF with other forms of fibrosing ILD that have, i.e. self-sustaining fibrosis, progressive decline in lung function, and early mortality in the group of “progressive fibrosing ILDs” that would describe ILD in patients who, independent of the classification of the ILD, at some point in time exhibit a progressive fibrosing phenotype. Pulmonary function parameters at a single time point do not reliably predict disease behavior and, despite multiple attempts, High resolution computer tomography (HRCT)-quantified disease extent on sequential imaging has not been established as a reliable marker of disease progression. Based on the results from a number of reports investigating Krebs von den Lungen-6 / Mucin 1 (KL-6/MUC1), the serum levels of KL-6/MUC1 are useful for (1) detecting the presence of disease, (2) evaluating disease activity, and (3) predicting outcomes in various types of ILDs.

1 Current Classification

ILD early and accurate diagnosis is challenging due to heterogeneity of the disease.

Even with multidisciplinary team assessment, 15-25% of ILD patients remain unclassifiable

Interstitial lung diseases (ILDs) represent a large, heterogeneous group of more than 200 different entities, most of which are classified as rare diseases. They are defined as lung diseases that affect the alveolar structures, the pulmonary interstitium, and small airways. The

current diagnosis of an ILD relies mainly on the combination of clinical, radiological, and pathological criteria, which should be explored in a multidisciplinary board [10].

Even if Interstitial Pulmonary Fibrosis (IPF) can be seen as the largest group within ILDs it has been shown that approximately one in 10 patients has an unclassifiable ILD. This makes it the fourth most common classification behind IPF (21%), hypersensitivity pneumonitis (15%) and sarcoidosis (14%) [21].

While multidisciplinary team assessment yields a definite diagnosis in many cases of interstitial lung disease, 15-25% of patients remain unclassifiable [1].

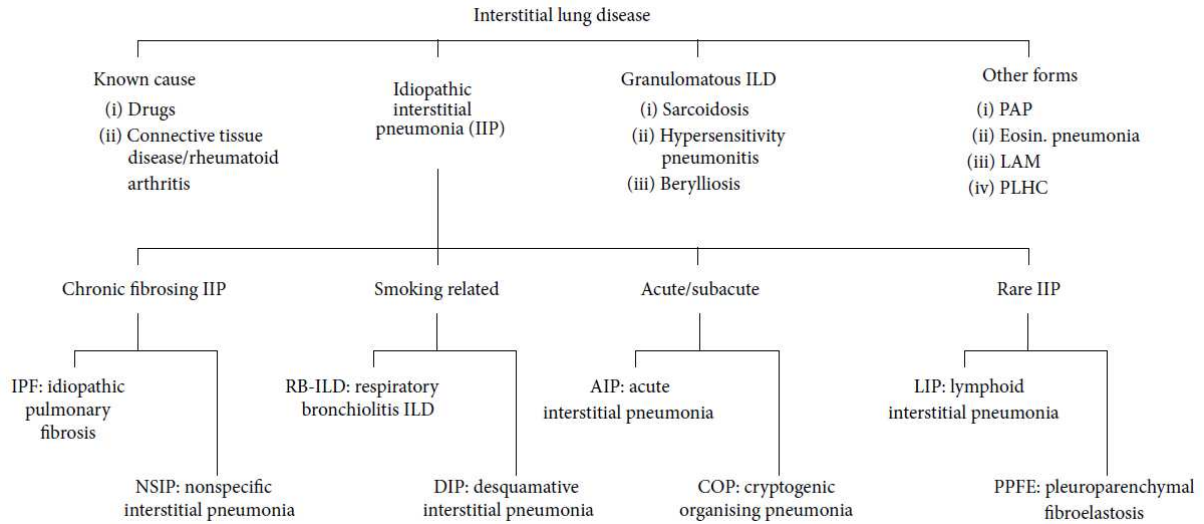


FIGURE 1 (from Kreuter 2015): Classification of ILDs. PAP: pulmonary alveolar proteinosis, LAM: lymphangioleiomyomatosis, and PLHC: pulmonary Langerhans cell histiocytosis. Adapted from the American Thoracic Society, European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias, *Am J Respir Crit Care Med.* 2002, and Travis et al. *Am J Respir Crit Care Med.* 2013

2 ILD diagnosis – current professional practice

2.1 The role of functional testing

HRCT scans plays an essential role in the diagnosis of ILDs

A variety of functional tests can be used to assess severity of fibrosis, such as a measurement of forced vital capacity (FVC) and gas exchange (i.e. diffusing capacity of the lung for carbon monoxide (DLCO)), and exercise capacity.

Forced vital capacity is a reliable, valid and reproducible measure of disease progression.

Decrease in FVC% pred. greater than 10% over a 12-month period have a significantly lower 5-year survival.

Yet, functional tests are not specific and overlapping between different fibrosing diseases.

Accurate diagnosis of IPF is critical, as other forms of ILD that have similar clinical presentations to IPF require different

treatment strategies. Imaging plays an essential role in the diagnosis of ILDs. Once known causes of ILD have been excluded, a usual interstitial pneumonia (UIP) pattern on high-resolution computed tomography (HRCT) is essentially diagnostic of IPF in the appropriate clinical setting. In addition, some non-UIP HRCT patterns strongly suggest an alternative diagnosis [3].

Progression of fibrosing ILDs is reflected in an increase in fibrosis evident on a computed tomography scan, a decline in forced vital capacity (FVC) and gas exchange (i.e. diffusing capacity of the lung for carbon monoxide (DLCO)), worsening of symptoms and exercise capacity, and deterioration in health-related quality of life. There is no consensus as to how disease progression should be defined in patients with ILDs.

Most clinical trials and observational studies in patients with ILDs have defined disease progression in terms of decline in FVC, measured as the change from baseline in mL or as a percentage of the predicted value, as a categorical change, or as a composite of categorical change and mortality [4].

Forced vital capacity (FVC) is a reliable, valid and reproducible measure of disease

progression in patients with IPF and change in FVC percentage predicted (FVC% pred.) over time is a well-established predictor of mortality. Indeed, it has been shown that patients who experience a decrease in FVC% pred. greater than 10% over a 12-month period have a significantly lower 5-year survival compared to patients whose FVC% pred. declines of 10% or less during the same period of time. While there is no universally agreed upon definition for these two clinical phenotypes, they are commonly referred to as “rapid” and “slow” progressors, respectively [2].

Functional tests give a good view on severity but are not specific, but common in all ILD with fibrosis.

Given their overlapping clinical, radiological and pathological presentations, the terminology recently used to describe patients with fibrosing ILDs that may present a progressive phenotype, despite currently available treatment, is “progressive-fibrosing ILD (PF-ILD)”.

2.2 Broader than IPF - Progressive fibrosing ILD

Fibrosis is the common feature of a variety of different ILDs.

Change from ILD classification related to the origin of the disease to a new way of classification in ILDs based on common features of diseases irrespective of the trigger for the fibrosis: progressive-fibrosing ILD.

IPF as “prototype” of progressive-fibrosing ILD.

Varying proportions of patients with ILDs develop a chronic progressive-fibrosing phenotype. IPF can be viewed as the prototype progressive-fibrosing ILD; it is relatively well understood both in terms of epidemiology and disease behavior [15]. In addition to IPF, fibrosing ILDs that may present a progressive phenotype include idiopathic nonspecific interstitial pneumonia, connective tissue disease-associated ILDs, hypersensitivity pneumonitis, unclassifiable idiopathic interstitial pneumonia, ILDs related to other occupational exposures and sarcoidosis [19].

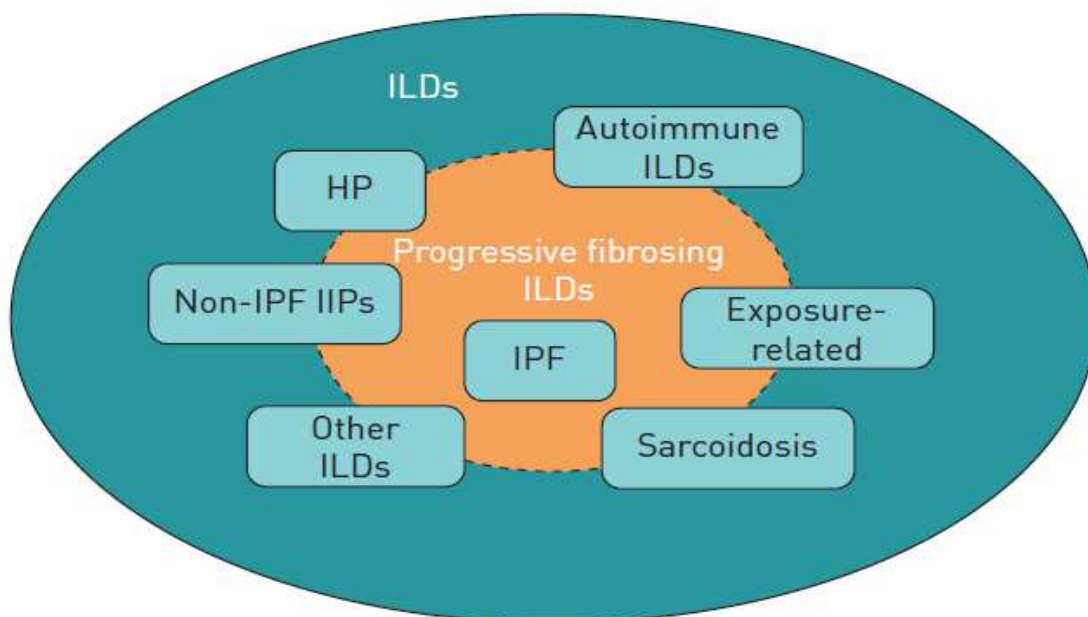


FIGURE 2 (from Cottin 2019 ERS Reviews): Types of interstitial lung disease (ILD) that may be associated with a progressive fibrosing phenotype. HP: hypersensitivity pneumonitis; IPF: idiopathic pulmonary fibrosis; IIPs: idiopathic interstitial pneumonias.

Whereas the current classification of ILDs is more related to the origin of the disease the question raises, if it wouldn't make sense to use the common features of diseases for a new way of classification in ILDs to give information for possible antifibrotic treatment irrespective of the trigger for the fibrosis.

Several scientific authors deal with the idea of combining IPF with other forms of fibrosing ILD that have, i.e. self-sustaining fibrosis, progressive decline in lung function, and early mortality in the group of "progressive fibrosing ILDs" that would describe ILD in patients who, independent of the classification of the ILD, at some point in time exhibit a progressive fibrosing phenotype. This approach could be done for the purposes of clinical research and, potentially, for treatment of patients with the

same symptoms regardless of the origin of the fibrotic disease. The presence of a UIP pattern also confers a worse prognosis than other patterns on HRCT in patients with IPAF and unclassifiable ILD. In a study of data from 144 patients with IPAF in a US registry, patients with a UIP pattern had similar survival to patients with IPF, while those with IPAF and patterns other than UIP had a similar survival to patients with CTD-ILDs. A greater extent of fibrosis on HRCT and worse lung function (FVC or DLCO) have also been shown to be predictors of mortality in patients with RA-ILD [4].

The commonalities of ILDs that may present a progressive-fibrosing phenotype suggest the potential for a common treatment pathway [5].

3 Use of serum biomarkers in progressive fibrosing ILDs

3.1 New dimension of progressiveness

Use of serum biomarkers can provide an incremental value in disease severity assessment and prediction, since

- several pulmonary conditions can confound the interpretation of PFT results.
- general health status often inhibits patients from properly performing PFT.
- serum markers can assess the disease activity and physiopathology dynamic.

Recent developments make it critical to rapidly identify patients whose disease will progress to extensive lung fibrosis.

Based on the results from a number of reports investigating KL-6/MUC1, the serum levels of KL-6/MUC1 are useful for (1) detecting the presence of disease, (2) evaluating disease activity, and (3) predicting outcomes in various types of ILDs. Because the measurement of serum KL-6/MUC1 levels is rapid, inexpensive, reproducible, less invasive, and easier to perform than SLB, HRCT, BAL, and pulmonary function tests, we believe that this biomarker would provide a significant benefit to the clinical management of patients with ILDs [8].

Pulmonary conditions, such as emphysema or pulmonary hypertension, combined with ILD, can confound the interpretation of PFT results. Furthermore, respiratory failure due to acute exacerbation of ILD often inhibits patients from properly performing PFT. In addition, the corresponding type of CTD-ILD suggested by HRCT is insufficient to evaluate the current disease status or predict disease progression [13].

With the recent development of new treatments for lung fibrosis, it is critical to

identify those patients who will develop lung disease at an earlier stage, and to rapidly identify those whose disease will progress to extensive lung fibrosis. Moreover, enriched populations of patients would facilitate clinical trials and the faster development of innovative therapies. To date, none of the abovementioned validated lung functional/radiologic measures or serologic markers would allow the prediction of progression of lung fibrosis over time in patients with Systemic Sclerosis (SSc); such measures could help individualize the management of specific risk in each patient. Therefore, there is a growing interest in identifying and use of biomarkers for the diagnosis of lung fibrosis, assessment of lung fibrosis severity and activity, and prognosis in patients with SSc who have already been diagnosed as having ILD [6].

Beyond the functional and imaging classification of disease progressing, due to

numerous data it gets more and more clear that there is a link between serum proteins and the presence or severity of ILD. Elevated serum Krebs von den Lungen-6 (KL-6) levels have been identified in several non-IPF ILDs, including NSIP, HP, CTD-ILD, and sarcoidosis [10]. Longitudinal analysis of serum KL-6 in a small cohort of patients with SSc showed that rapidly increasing levels of KL-6 were associated with new onset or progressive fibrosis, whereas stable KL-6 levels were associated with stable disease.

In patients with SSc-ILD, Kennedy and colleagues also identified KL-6 as a biomarker that could prospectively predict lung function decline in these patients. Results from a more recent study by Salazar and coworkers support the notion that higher baseline KL-6 levels are predictive of more active disease, which is associated with subsequent deterioration of lung function and the development of respiratory failure.

3.2 KL-6 biochemical properties

KL-6 is a specific epitope of the heavily glycosylated mucin 1 protein

Mucin 1 is identical CA 15-3.

CA 15-3 - marker for monitoring early recurrence of different conditions including ILDs as well as breast cancer.

KL-6 - specific marker for MUC1 expression by the lung tissue.

KL-6/MUC1 is detectable in the serum of patients with ILD, and extensive investigations performed primarily in Japan have revealed that serum KL-6/MUC1 is elevated in 70-100% of patients with various ILDs, including idiopathic interstitial pneumonias, collagen vascular disease-associated interstitial

pneumonia, hypersensitivity pneumonia, radiation pneumonitis, drug-induced ILDs, acute respiratory distress syndrome, pulmonary sarcoidosis, and pulmonary alveolar proteinosis [23]. The results from various studies have supported the utility of KL6/MUC1 as a serum biomarker for detecting these various ILDs. Moreover, KL-6/MUC1 serum levels have been demonstrated to be useful for evaluating disease activity and predicting the clinical outcomes of various ILD types [8].

Ishikawa et al. clearly demonstrated that based on the results of a carbohydrate composition analysis KL-6 is a sub molecule of MUC1.. In accordance with these different observations, KL-6/MUC1 is commonly used to denote the KL-6 molecule. The possible carbohydrate epitopes of the anti-KL-6 mAb have been reported to be novel O-linked glycans containing 60 sulfo-Gal/ GalNAc of MUC1.

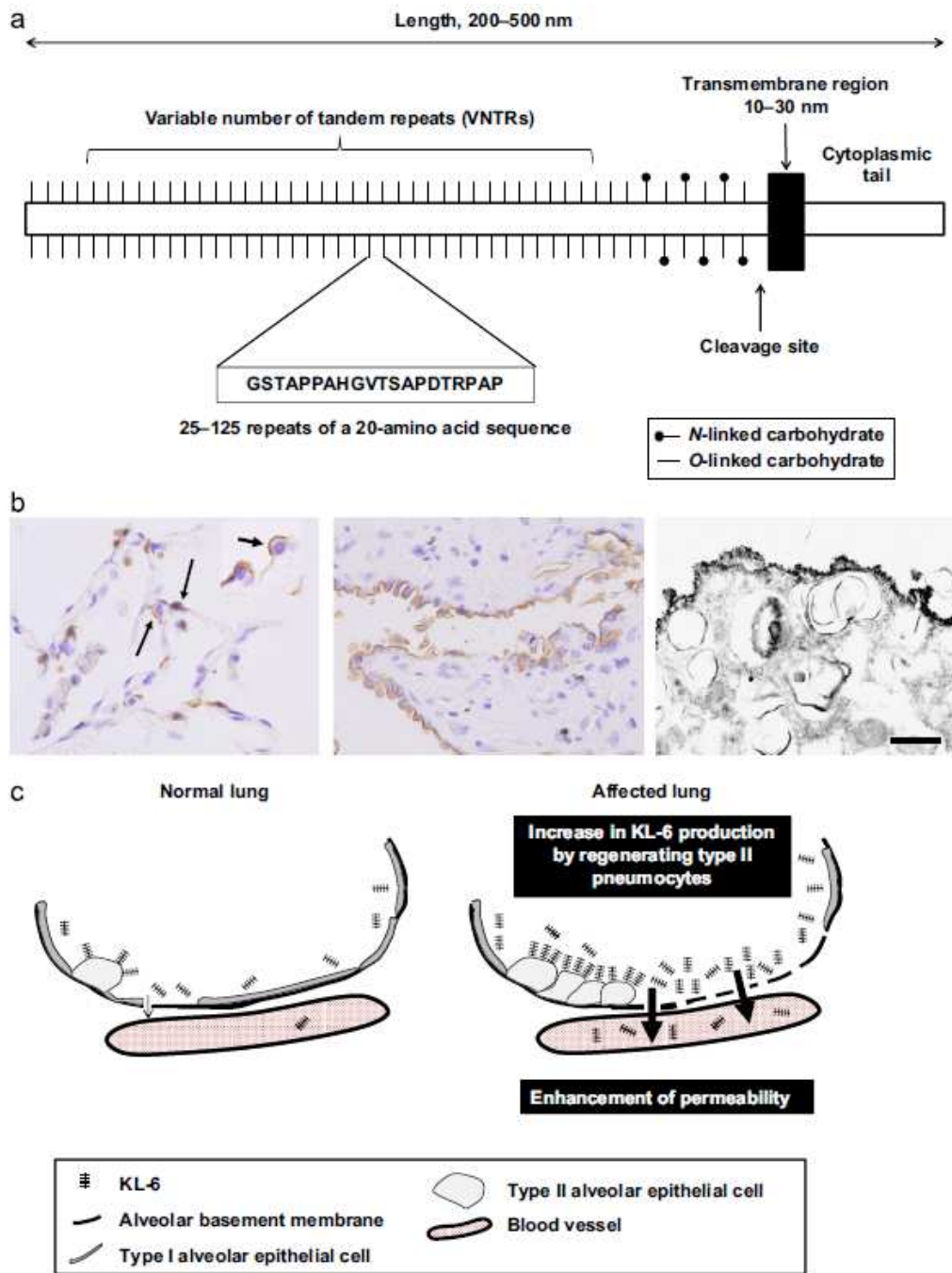


FIGURE 5 (from Ishikawa 2012): (a) Structure of MUC1. MUC1 is a large glycoprotein that contains 3 domains: (1) a cytoplasmic tail, (2) a single transmembrane region, and (3) an extracellular domain. The extracellular region contains sites of O- and N-linked glycosylation and a variable number tandem repeat (VNTR) domain of 20–100 repeats of a 20 amino acid sequence, (b) KL-6/MUC1 expression on the surface of type II pneumocytes. A discontinuous positive reaction (arrows) with anti-KL-6 antibody was observed in presumably normal lung tissue from a case of pneumothorax (left panel; magnification, $\times 400$). Note the distinct dome-shaped positivity of the type II alveolar cells on staining with KL-6 antibody (inset at left panel; magnification, $\times 800$). Linear and continuous staining for KL-6/MUC1 was observed on the cell surface of regenerating type II pneumocytes in patients with IPF (middle panel; magnification, $\times 400$). Immunoelectron microscopic findings revealed that the reaction with anti-KL-6 antibody exhibits a linear pattern on the cell surface of type II pneumocytes in a patient with NSIP (right panel; magnification, $\times 400$). Note that positive surface granular structures are approximately 100–200 nm in diameter. Scale bar $\frac{1}{4}$ 0.5 μ m. Modified from, with permission from the publisher. (c) Mechanism for the blood uptake of KL-6/MUC1. The increased serum levels of KL-6 in patients with ILDs may be due to an increase in KL-6 production by regenerating alveolar type II pneumocytes and/or enhanced permeability following the destruction of alveolar capillaries in the affected lung.

All these results support the hypothesis that KL-6/MUC1 is one of the key molecules involved in the intra-alveolar fibrotic process and pulmonary fibrosis. Moreover, these results indicate that KL-6/MUC1 may become a promising molecular target for the treatment of pulmonary fibrosis [8].

KL-6 is a commercially available monoclonal antibody raised against a specific epitope of the heavily glycosylated mucin 1 protein. In the literature, however, the term KL-6 is commonly used to indicate the protein, rather than the antibody.

Mucin 1, encoded by the MUC1 gene, is identical to the target molecule to which antibodies have been developed collectively known as CA 15-3. The CA 15-3 assay utilizes a couple of antibodies which are directed against a unique variable-number tandem repeat on the protein backbone (DF3) and a carbohydrate epitope on that repeat (115D8). CA 15-3 and commercial kits alike are currently being used

as markers for monitoring early recurrence of breast cancer, while KL-6 has been claimed to be specific to MUC1 expression by the lung tissue. The latter is supported by studies reporting that KL-6 specifically recognizes mucin 1 that is derived from type II pneumocytes following injury and subsequent regeneration [12].

Both epitopes of CA15-3 and KL-6 exist in different positions of MUC1 expressed on the surface of various epithelial cells. MUC1, classified as a member of the mucin family, is a high molecular weight glycoprotein rich in O-glycosylated serine and threonine residues. The upregulated expression of MUC1 has been noted in breast and lung adenocarcinomas. Monoclonal antibody for BCA225 is the same as that recognizing CA15-3. KL-6, BCA225 and CA15-3 are all recognized as members of the mucin family [Ri 2009]. Glycosylation at Thr/Ser residues of the tandem-repeating MUC1 peptides appears to determine the disease-associated antigenic structures of KL-6 [14].

4 KL-6 in disease prognosis

4.1 Clinical cut-off values for identification and prognosis

A clinical cut-off value of 500 U/mL has been established for distinguishing patients with ILDs from healthy subjects and patients with lung diseases other than ILDs.

Disease progression is significantly faster in patients with ILDs with KL-6/MUC1 > 1000 U/mL at initial measurement.

patients with IPF with initial KL-6 >1000 U/ml have a poor prognosis and higher risk of acute exacerbation.

Recent research has shown that serum and bronchoalveolar lavage fluid level of KL-6 has an important value in the diagnosis, treatment assessment and prognosis prediction. It has been demonstrated that KL-6 level has a negative correlation with DLCO, which is consistent with the previous studies. Bonella et al. reported that serum KL-6 level was increased in 33 cases of pulmonary alveolar proteinosis; the increase of KL-6 was also positively correlated with pulmonary function markers. Higher serum KL-6 levels were associated with worse pulmonary function in these patients. Staples et al. found that CT scan scores correlated significantly with clinical and functional severity of interstitial disease. It has been proven that HRCT scores in IPF patients were independently predictive of mortality. Quantification of the morphologic extent of disease on HRCT has, however, remained

difficult to incorporate into routine practice, mainly because of costs and radiation-exposure limit repeatability over time. To the best of our knowledge, the present study is the first one which proved that serum KL-6 level has a positive correlation with the HRCT score in patients with ILD, indicating that KL-6 might be a valuable marker for assessment of the extent of ILD. KL-6 analysis could greatly reduce the risk of X-ray exposure and is much easier and more acceptable for patients, when used to monitor the therapeutic effect and disease severity [17].

A clinical cut-off value of 500 U/mL has been established for distinguishing patients with ILDs from healthy subjects and patients with lung diseases other than ILDs whereas elevated serum KL-6/MUC1 (KL-6/MUC1 levels >1000 U/mL) in IPF patients at the initial visit were associated with increased mortality. Satoh et al. also reported that the progression of the disease was significantly faster in patients with ILDs whose KL-6/MUC1 levels were 1000 U/mL or more at the initial measurement than in patients whose KL-6/MUC1 levels were less than 1000 U/mL [8].

It has been shown that patients with IPF with initial KL-6 >1000 U/ml have a poor prognosis,

and this was confirmed by case studies. Compared to patients with initial KL-6 <1000U/ml, those with initial KL-6 >1000 U/ ml tended to have a higher frequency of acute exacerbation, although there was no significant difference in the yearly decline of Δ FVC and % Δ FVC between those 2 groups. In 2014 Oshimo et al. reported that the frequency of acute exacerbation was high among cases with high initial KL-6 levels [16]. Thus, acute exacerbation may be highly associated to the poor prognosis of patients with initial KL-6 >1000 U/ml. These findings suggest that assessing initial serum KL-6 levels, which can predict acute exacerbation, and patterns of serial changes in serum KL-6 levels, which correlate to disease progression, could be useful for assessing the prognosis of IPF. Patients with both initial KL-6 <1000 U/ml and no serial increase in KL-6 (i.e., the non-increased KL-6 group) had a better prognosis than those with serum KL-6 >1000 U/ml or the increased KL-6 group with initial KL-6 <1000 U/ml. Although initial KL-6 <1000 U/ml is considered associated with a good prognosis, our findings suggest that changes over time in serum KL-6 levels can be even more strongly associated with poor prognosis than low initial levels [22].

4.2 KL-6 as risk parameter for ILD in CTD/autoimmune patients

In connective tissue diseases, Krebs von den Lungen-6 (KL-6) is sensitive for ILD detection and activity assessment.

Serum KL-6 levels were increased in patients with CTD-ILD and have a positive correlation with ILD severity.

Serum KL-6 levels have a negative correlation with PFT parameter.

The main pathogenesis is aberrant recovery of epithelial injury and collagen deposition. Fibrotic nonspecific interstitial pneumonia, connective tissue disease (CTD) especially rheumatoid arthritis (RA) associated ILD, and chronic hypersensitivity pneumonia (CHP) are important differential diagnosis. Main symptoms are non-productive cough and progressive exertional dyspnea. Crucial physical findings are scalene muscle hypertrophy, bibasilar fine crackles, and finger clubbing. The serum markers such as lactate dehydrogenase (LDH) and KL-6 are sensitive for ILD detection and activity assessment [9].

The authors of a retrospective study, comparing groups of patients with CTD with

and without ILD, and performing a correlation with functional parameters as well as with a semiquantitative CT grading conclude that Serum KL-6 could be a clinically useful biomarker in screening and evaluating CTD-ILD. As the results showed that serum KL-6 levels were increased in patients with CTD-ILD and had a positive correlation with ILD severity as measured using a semiquantitative CT grading scale, whereas serum KL-6 levels had a negative correlation with PFT parameters [13].

KL-6 may have a substantial role for evaluating ILD among CTD patients. Evaluation of ILD through regular chest HRCT for patients with SSc or IM can be justified because of the relatively high prevalence and potential life-threatening course in this patient population.

However, for other CTDs, such as RA, SS, and SLE, established epidemiological data, including the incidence, prevalence, and outcome of ILDs, are lacking; therefore, regular chest HRCT for patients with these CTDs is not currently recommended. Considering cost-effectiveness and radiation hazard, KL-6 measurement by simple blood test would be a good alternative to chest HRCT for evaluating the current status of ILD in rheumatology clinics regardless of the CTD type [13].

KL-6 has been approved by Japan's Health Insurance Program as a diagnostic marker for ILDs since 1999, and KL-6 levels are examined in more than 2,000,000 samples per year in Japan [8].

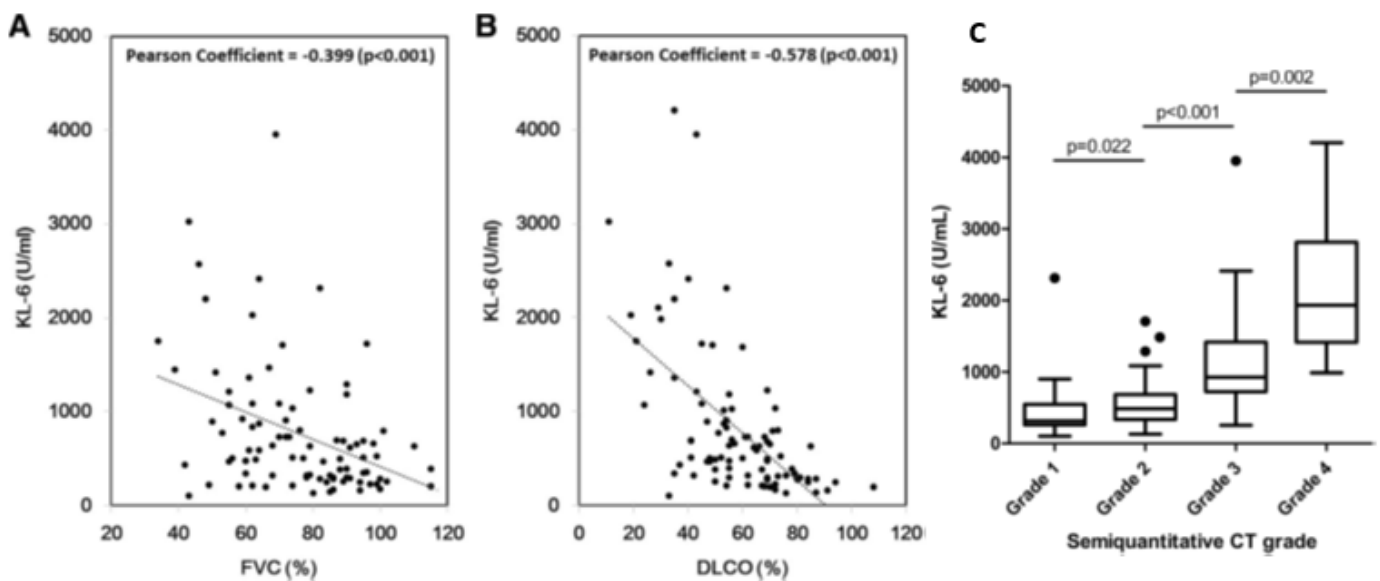


FIGURE 3 (from Lee2019): Association between serum KL-6 level and

A FVC% or

B DLCO% of patients with ILD. DLCO%, diffusing capacity of carbon monoxide % predicted; FVC%, forced vital capacity % predicted; ILD, interstitial lung disease

C: Serum KL-6 levels of ILD patients according to semiquantitative CT grades. CT, computed tomography; grade 1, 0–25% involvement of ILD on chest CT; grade 2, 26–50%; grade 3, 51–75%; grade 4, 76–100%

5 From Classification to disease activity

5.1 Emergence of a new paradigm for assessing disease activity in chronic pulmonary fibrosis

Focus on disease activity instead of classification.

KL-6 can help to get a clearer picture of the pathophysiological proceedings in the lung and the disease activity that lead to different courses of the disease.

While IPF is the classic fibrosing ILD, clinical data suggest that there is a larger group of patients with differing clinical ILD diagnoses who develop a progressive fibrosing phenotype during the course of their disease. These patients demonstrate a number of similarities

to IPF, with their disease being defined by the presence of progressive pulmonary fibrosis, worsening respiratory symptoms, declining lung function, resistance to immunomodulatory therapies and, ultimately, early mortality. These patients can be described as patients with progressive fibrosing interstitial lung disease [7].

Pulmonary function parameters at a single time point do not reliably predict disease behavior and, despite multiple attempts, HRCT-quantified disease extent on sequential imaging has not been established as a reliable marker of disease progression [20]. Serum biomarkers, such as KL-6 can help to get a clearer picture of the pathophysiological proceedings in the lung and the disease activity that lead to different courses of the disease.

With KL-6 we don't focus on different classes within ILD but on the severity and activity of the disease.

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