Literature Review

Krebs von den Lungen-6 (KL-6) and Surfactant-D as Biomarkers of Interstitial Lung Disease: A Literature Review

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Abstract

Interstitial Lung Disease (ILD) is a group of lung diseases characterized by various patterns of lung tissue damage, including inflammation and fibrosis of the lung interstitium, both with known or unknown causes (idiopathic). In establishing the diagnosis of ILD, a comprehensive approach including history-taking, physical examination, and supporting examinations, is needed and managed in a multidisciplinary manner. Biomarkers are diagnostic tools known to be accessible, inexpensive, reproducible, and non-invasive for helping diagnose ILD patients. Growing evidence has supported the idea that many biomarker molecules can detect lung injury in ILD, including Krebs von de lungen-6 (KL-6) and Surfactant D (SP-D). KL-6 and SP-D could be utilized in the detection, disease monitoring, prognostication, and therapeutic responses of ILD patients. This review aimed to discuss several potential Kl-6 and SP-D biomarkers against ILD and discusses their clinical utility.

Keywords: Biomarker, Interstitial Lung Disease, KL-6, Surfactant D

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INTRODUCTION

Interstitial Lung Disease (ILD) is a group of lung diseases characterized by various patterns of lung tissue damage, including inflammation and fibrosis of the lung interstitium, both with known or unknown causes (idiopathic).[1] Some examples of ILDs include idiopathic interstitial pneumonia or idiopathic pulmonary fibrosis (IIP/IPF), collagen-vascular disease-associated interstitial pneumonia (CVD-IP), chronic hypersensitivity pneumonia (CHP), radiation pneumonitis, drug-induced PPIs (PPI-D), acute respiratory disease syndrome (ARDS), and sarcoidosis.[2]

In making the diagnosis of ILD, a comprehensive approach is needed, including history-taking, physical examination, and supporting examinations. Multidisciplinary discussion is one way to establish a diagnosis so as to provide more appropriate therapy. Imaging modalities are necessary in diagnosing ILD, for example, High Resolution Computational Tomography (HRCT) Scan. Other investigations needed are bronchoscopy and invasive lung biopsies, which require special medical facilities. Therefore, diagnostic modalities that are accessible, inexpensive, reproducible, and non-invasive are needed, one of which is biomarker.[3]

Biomarkers are one of the diagnostic tools that could improve the limitations of existing modalities. A biological marker is a biological substance used as a unique, measurable marker as an indicator of the biological process of a disease that is useful in the process of diagnosis, prognosis, and evaluating therapy response. Biomarkers are often used to assist clinicians in predicting the course of the disease because it is considered a less invasive, relatively safer, and faster procedure.[1]

ILD biomarker modalities might include pulmonary function test results, imaging, molecules detected in the blood, bronchoalveolar lavage fluid (BALF), or lung tissue. ILD damages lung tissue and

activates the scar tissue formation process, and release biological molecules. Some of the biomarkers that are strong candidates for the detection of ILDs are as follow:[4,5]

1. Markers of alveolar epithelial cell damage and dysfunction (KL-6, SP-A, and SP-D)
2. Aberrant fibrogenesis and matrix remodeling (MMP7, MMP3, LOXL2, HSP47, IGFBPs, periostin, circulating fibrocytes, fibrillin-1, osteopontin)
3. Endothelium damage (IL-8, ET-1, VEGF)
4. Inflammation and upregulated immunity (CCL18, YKL-40, ICAM, VCAM, E-selectin, IL-6, CXCL-13, anti-HSP70 IgG, BLyS, serum RAGE).

This literature review will discuss two biomarkers for detecting lung tissue damage in ILD: Krebs von den lungen-6 (KL-6) and Surfactant Protein D (SP-D). KL-6 and SP-D are two markers that can be examined when there is an alveolar epithelial cell damage and dysfunction. KL-6 in humans is classified as mucin or Cluster 9 (MUC1 protein) in the form of a high molecular weight glycoprotein that circulates in the blood. KL-6 can be detected by blood and bronchoalveolar lavage (BAL) analysis. KL-6 is expressed on the extracellular surface of type II alveolar and bronchiolar epithelial cells.[6]

KL-6/MUC1 is a glycoprotein containing three large domains, including (1) a cytoplasmic tail, (2) a single transmembrane region, and (3) an extracellular domain. KL-6/MUC1 has a relatively rigid structure, extends outward to 200-500 nm above the plasma membrane, and is found on the apical crest or surface of glandular epithelial cells. So far, the clinical importance of KL-6/MUC1 has not been established. However, in an experimental study, KL-6 became an agent that promoted migration, chemotactic activity, proliferation, and survival of pulmonary fibroblasts. Furthermore, this molecule has additive properties to transforming growth factor (TGF-β).[6]

Surfactant is a substrate in lung parenchyma tissue synthesized by Clara cells and alveolar epithelial cells that line the lung epithelium. The primary function of surfactants is to reduce the tension between the air and liquid surfaces, make the lungs easy to expand during inhalation, and prevent collapse on exhalation. SP-D is one of surfactant type that often studied and assessed to have diagnostic and prognostic properties. SP-D is a subgroup of the superfamily C-type collectin. Like other surfactants, SP-D reduces surface tension and plays a vital role in the innate lung immune system. The concentration of SP-D in serum indicates pathological damage to the lung, which causes SP-D migration from the alveolar space to the blood vessels.[7]

KREBS VON DEN LUNGEN-6 (KL-6) AND SURFACTANT-D AS BIOMARKERS OF IDIOPATHIC PULMONARY FIBROSIS

IPF is the etiology of ILD, whose cause is unknonw, in the form of interstitial pneumonia. Recent research shows no biomarkers capable of diagnosing, predicting disease progression, or evaluating the response to therapy.[8,9] KL-6 has been found to positively correlate with IPF, as stated by Bonella et al at the 2015 ATS conference.[10] Furthermore, KL-6 is also helpful in assessing the response to therapy with nintedanib and pirfenidone.[10–12] Yokoyama et al assessed that KL-6 detected early in the course of the disease (above or below 1000 U/ml) could help predicting patient outcomes.[13]

KL-6 has a good performance in assessing the survival of patients with a high cut-off (>1,000 U/ml) which is considered to have a pretty good predictive value compared to a low cut-off, as suggested by Ishii et al and Satoh et al. Fluctuations in KL-6 levels were also considered to help in predicting disease progression.[14,15]

This finding indicates that serial examinations (change cut-off >1,000 U/ml) help assess and monitor the patient's prognosis over time. KL-6 is a more specific biomarker in diagnosing IPF than sarcoidosis, hypersensitivity pneumonia, and connective tissue disease. The finding of high KL-6 levels was also associated with decreased forced vital capacity (FVC) and carbon monoxide diffusion capacity (DLCO) values.[16]

Administration of antifibrotic therapy was also positively correlated with KL-6 in predicting response to therapy. Okuda et al reported that pirfenidone had an attenuating effect on the aggravation of VVC. This finding is supported by a change in FVC 50 cc in the 6-month post-therapy period and correlates with KL-6 and SP-D.[17] Koga et al reported that pirfenidone has good efficacy and normalizes KL-6 levels in patients.[18]

Another benefit is the association of KL-6 with the incidence of acute exacerbations in IPF patients. Oshimo et al reported that KL-6 levels with a cut-off of 1,300 U/ml could predict acute exacerbations.[19] Another study by Matsuzawa et al of oxidative stress markers discovered that the cut-off of 1,810 U/ml was closely related to the incidence of acute exacerbations in IPF.[20] However, due to the limitations of existing studies, it is still unclear how KL-6 relates to acute exacerbations.

The potential of SP-D as a biomarker was seen in the PROFILE cohort study. SP-D showed a difference in results between SP-D BAL and SP-D serum. SP-D BAL was decreased in IPF patients, while in SP-D serum, there was an increase in levels compared to control patients.[21] Furthermore, SP-D levels in IPF patients were more elevated than in other ILD diseases. Majewski et al stated that SP-D had a pretty good diagnostic value in differentiating IPF patients from controls (AUC=0.9089; 95% CI=0.8196-0.9983) with a sensitivity of 100% and specificity of 75% at a cut-off of 12,180 ng/ml.[22]

Elevated serum SP-D is also known to correlate with mortality in IPF patients. In 2017, a meta-analysis and systematic review discussed the relationship of SP-D to the prognosis of IPF patients. The risk of death in patients with elevated SP-D levels in IPF patients increased to 111% (HR=2.11 95% CI=1.60-2.78; Z-Value=5.31; *P*<0.001; I2=0.0%). Moreover, the differences in SP-D levels were not significantly different in Asian or Caucasian populations. In summary, SP-D is useful in predicting patient outcomes and has the potential to be a widely accepted biomarker regardless of race.[23]

Serial SP-D measurements are valuable in monitoring response to antifibrotic therapy and assessing disease progression. The PROFILE study revealed a difference in SP-D levels at three months in patients with Progressive Disease versus Stable Disease (46.6 ng/ml vs. 34.6 ng/ml).[21] Majewski et al reported that SP-D levels were significantly increased in the same group of patients as in the PROFILE study in patients treated with antifibrotics for two years (Cut-off Progressive Disease vs. Stable Disease, 494.5 (95% CI=297.3-640.1) ng/ml vs. 271.9 (95% CI=188.2-470.7) ng/ml; *P*<0.05).[22]

In a multicenter study in Japan, serum SP-D was found to be helpful in assessing response to pirfenidone antifibrotic therapy. In contrast, clinical improvement at 52 weeks post-therapy (vital lung capacity) was found in the group with a cut-off <202 ng/ml (*P*=0.0949) and extended Progression-Free Survival.[24]

KREBS VON DEN LUNGEN-6 (KL-6) AND SURFACTANT-D AS BIOMARKERS OF PNEUMOCONIOSES

Asbestosis and silicosis are progressive forms of pneumoconiosis and are characterized by interstitial fibrosis due to exposure to asbestos and silica dust. The current clinical detection and diagnosis of pneumoconiosis still depend on a history of occupational exposure and abnormalities found on radiological examination. Although research data is still limited, KL-6 and SP-D are known to be potential biomarkers in asbestosis and silicosis cases, both in experimental studies and observational studies. KL-6 and SP-D in cases of pneumoconiosis could help assessing disease progression.[25]

Xue et al evaluated the association between serum KL-6 and pneumoconiosis such as asbestosis and silicosis. Serum KL-6 was found to have significantly higher values than in healthy and dust-exposed patients without pneumoconiosis. In addition, serum KL-6 was positively correlated with fibrosis score on HRCT and negatively correlated with %predicted FVC and %predicted DLCO. In the diagnostic aspect, KL-6 had sensitivity, specificity, and AUC of 88.4%, 73.1%, and 0.874, respectively, with a cut-off of 216 U/ml in diagnosing asbestosis. KL-6 was very useful for differentiating patient with

pneumoconiosis, with a specificity of 81.2% and a cut-off value of 0.751/ml.[26]

It can be concluded that KL-6 has the potential to help exclude differential diagnosis and monitor the course of pneumoconiosis, especially in pneumoconiosis with a reasonably high progression rate, such as asbestosis and silicosis. Another study by Liu et al indicated that KL-6 helped predict the progression of silicosis. In patients exposed to silica, KL-6 was found to be significantly increased (P<0.01), but after the patient developed silicosis, serum levels of KL-6 decreased (P<0.01).[27]

Xue et al also investigated the association between asbestosis and silicosis on SP-D serum levels. Asbestosis patients significantly increased SP-D levels compared to silicosis patients, patients exposed to dust without disease, and controls (P<0.05). Blood levels of SP-D were also negatively correlated with the predicted %DLCO, which indicated that SP-D was closely associated with decreased diffusion function (P<0.05). However, SP-D did not have a better diagnostic value than KL-6 in including asbestosis patients (sensitivity of 65.1%, specificity of 76.9%, AUC of 0.757), but could still include cases of pneumoconiosis, especially silicosis and asbestosis, and excluded cases of non-pneumoconiosis (sensitivity of 46.6%, specificity of 88.2%, AUC of 0.657).[26]

Increased levels of SP-D were also found in limestone, cement, and coal workers. Andarini et al conducted a cross-sectional study and assessed SP-D levels in limestone miners (n=65), which showed an increase in serum SP-D levels in the exposed group.[28] Jalil et al also found similar findings in the cement-exposed population (n=61).[29] Furthermore, a case-control study by Zhou et al obtained the increased serum and BAL fluid SP-D levels and concluded that increased SP-D in BAL serum and fluid could increase the risk of coal-worker pneumoconiosis (CWP) (OR 77.91; 95% CI: 5.64-161.64).[30] Almost every patient with pneumoconiosis or exposure to inorganic substances has elevated SP-D levels. Further studies are needed to explore the role of SP-D in predicting the progression of pneumoconiosis cases.

KREBS VON DEN LUNGEN-6 (KL-6) AND SURFACTANT-D AS BIOMARKERS OF SARCOIDOSIS

Sarcoidosis is a chronic, multisystem disease of unknown cause with various clinical presentations, characterized by non-necrotizing granulomatous inflammation. Using biomarkers in sarcoidosis patients is beneficial for avoiding lung biopsies to monitor disease progression. KL-6 has been extensively studied in serum and BAL samples.[31,32]

Several studies have identified that KL-6 has higher levels in sarcoidosis patients than in controls. The Janssen study suggested that KL-6 is the best biomarker for differentiating sarcoidosis patients from healthy patients. In sarcoidosis patients, the fibrotic phase was found to have the highest levels of KL-6 compared to other phases. KL-6 levels also indicate differences in phenotype, clinical presentation, and localization of sarcoidosis.[33]

The study of d'Alessandro et al also confirmed that KL-6 in BAL was correlated with the CD4+/CD8+ ratio. This ratio was used to differentiate sarcoidosis and other ILD with a cut-off of 221 U/ml (specificity of 73% and sensitivity of 69%).[34] Sarcoidosis patients also showed a significant relationship with SP-D serum levels by the ELISA method. Beketov et al found that patient progression of sarcoidosis significantly correlated with serum SP-D levels (P<0.05).[35]

KREBS VON DEN LUNGEN-6 (KL-6) AND SURFACTANT-D AS BIOMARKERS OF CHRONIC HYPERSENSITIVITY PNEUMONITIS (CHP)

Chronic hypersensitivity pneumonitis is a granulomatous disease limited to the lungs caused by inhalation of antigens caused by specific environmental or occupational exposures. Patients with CHP may present with an acute, subacute, or chronic clinical presentation. Studies that discuss the KL-6 marker and the incidence of CHP are minimal. Nukui et al showed that serum KL-6 was increased in CHP patients due to exposure to poultry compared to healthy patients.[36] In addition, the usefulness of serum KL-6 was demonstrated in a study by Okamoto et al, where KL-6 levels may be elevated compared

to IPF and sarcoidosis patients, thus aiding in differential diagnosis and patient management. The cut-off limit agreed, in this case, was 1,500 U/ml to differentiate the three patients' differential diagnoses.[37]

Moreover, the potential of KL-6 as a prognostic factor in CHP patients was shown in farmer's lung disease, where there was a change in the percentage of DLCO in this group of patients compared to controls. So far, there are no studies discussing KL-6 in BAL. As with KL-6, in observational studies, SP-D was increased in cases of CHP, with a median of 264 ng/dl.[38] Janssen et al (n=49) expressed that, in addition to increased serum SP-D levels in bird fancier's lung patients, the ROC in this study yielded significant results in differentiating patients from controls.[39]

In a cohort study, Onishi et al revealed that SP-D can be used to diagnose chronic summer-type hypersensitivity pneumonitis (C-SHP) caused by *Trichosporon asahii* (*T. asahii*). Onishi et al proposed diagnostic criteria for C-SHP based on *T. asahii* antibody positivity (TaAb), a typical HRCT Scan for C-SHP, and KL-6 levels >1,500 U/ml or SP- D >250 ng/ml. If these three data points were found, the AUROC was 0.993. It can be concluded that SP-D might discriminate against other ILDs to diagnose CHP.[40]

From a prognostic point of view, a moderately high level at onset positively correlates with worsening pulmonary function. As an addition, avoiding allergens has decreased serum SP-D levels, indicating that SP-D helps monitor patient clinical improvement.[41] This result is controversial with the findings in the study of Kujecko et al that low SP-D levels gave a poorer clinical features (lower FEV-1 and FVC).[42] Despite the smaller number of participants, well-designed studies with more participants must confirm these findings.

SP-D is also helpful in assessing clinical improvement after steroid administration. One month of prednisolone administration at a dose of 0.5 mg/kg, CHP patients experienced a decrease in SP-D (SP-D started therapy vs. 1-month post-therapy: 287 ng/ml vs. 171 ng/ml, P<0.0001). In brief, SP-D can assist in monitoring the response to therapy given to patients.[37]

KREBS VON DEN LUNGEN-6 (KL-6) AND SURFACTANT-D AS BIOMARKERS OF CONNECTIVE TISSUE DISEASE – ILD

The incidence of ILD in connective tissue disease (CTD) patients is relatively high, estimated to reach 15%.[43] One of the studies discussing the relationship of CTD to KL-6 was presented by Nakajima et al, where KL-6 can help predict pulmonary interstitial involvement in CTD patients and can potentially be a biomarker of disease activity.[44] A study found that rheumatoid arthritis patients had a close relationship with serum KL-6 levels, which significantly correlated with high KL-6 levels in patients with pulmonary involvement.[45] Furthermore, KL-6, through other studies, has also been helpful in cases of ILD polymyositis/dermatomyositis and systemic sclerosis.[46,47] Bonella et al also obtained that scleroderma patients could benefit from the KL-6 ELISA in establishing the diagnosis of this disease.[10] This evidence is supported by a strong association between HRCT-fibrosis scores on disease activity and skin involvement.

The role of SP-D in CTD cases with ILD is still limited, most of which have been reported in patients with systemic sclerosis, dermatosis/polymyositis, and rheumatoid arthritis. Several studies have found that serum SP-D levels are increased in patients with systemic sclerosis compared to healthy patients.[48]

In addition, closely related to diagnostic and prognostic aspects, there are data discrepancies in some studies. There is a large prospective study with a sample size of 427 ILD patients among patients with systemic sclerosis. SP-D with a combination of anti-topoisomerase I antibodies can detect the presence of ILD with a sensitivity of 97%, specificity of 69%, a positive predictive value of 80%, and a negative predictive value of 95%. With the combination of these two biomarkers, the study could divide patient groups into three categories based on the risk of ILD: mild risk (30–44%), moderate risk (45–

70%), and high risk (>70%). However, these results did not show a significant correlation between SP-D and the degree of lung damage, evolution, or direct patient mortality.[49] From a therapeutic point of view, systemic sclerosis patients receiving cyclosporine and prednisolone showed decreased SP-D levels, indicating an excellent response to therapy with a cut-off of <200 ng/ml.[50] Due to the limited sample size, a large prospective observational study is required to confirm these findings.

In dermatomyositis/polymyositis patients, SP-D helps predict patient mortality. SP-D levels were found to be higher in non-survivor patients than in survivors. SP-D levels in the non-survivor group were relatively high, reaching 110 ng/ml, with the highest mortality in the concentration of 127.6 ng/mL. Although the population is small, this still indicates the potential for SP-D in cases of dermatomyositis/polymyositis, and further studies of good quality are needed.[51]

Zhong et al conducted a meta-analysis on the diagnostic accuracy of SP-D in several cases of CTD with ILD. This study collected several studies discussing systemic sclerosis, dermatosis/polymyositis, and rheumatoid arthritis. In this study, SP-D had sensitivity to diagnosis systemic sclerosis and dermatosis of about 66% and 45%, and specificity of 83% and 93%, respectively. Although the results of this meta-analysis represent a fairly good diagnostic potential of SP-D, the heterogeneity and different subgroup analyses in the included studies preclude caution in their interpretation.[52] A significant limitation of this review is that the KL-6 and SP-D were chosen according to the author's opinion based on their potential utilization. In addition, some fields lack longitudinal studies and are not explored, including the role of KL-6 and SP-D in the acute exacerbation of ILD patients.

CONCLUSION

Based on the available studies, KL-6 and SP-D are predictive biomarkers that are useful in a wide range of diagnostic and management tasks for ILD patients. KL-6 and SP-D examinations can be used for ILD patients screening, so they are often used for early detection of this disease. For management, KL-6 and SP-D examinations are usually used to evaluate treatment.

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CONFLICT OF INTEREST

The authors affirm no conflict of interest.

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