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Clarisse André Freitas Marques Campos

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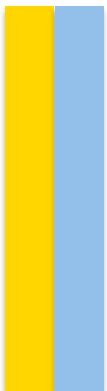

The Role of Krebs von den Lungen-6 as a Serum Biomarker in Interstitial Lung Disease: a review

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Declaration of Scientific Integrity

I, Clarisse André Freitas Marques Campos, nº 201807739 of the Integrated Master's Degree in Medicine of the Instituto de Ciências Biomédicas Abel Salazar of the University of Porto, declare that this dissertation is my own and has not been previously used in any other course or curricular units, from this or another institution. References to other authors (statements, ideas, thoughts) scrupulously respect the attribution rules and are dully indicated in the text and bibliographical references, per the referencing rules. I am aware that the practice of plagiarism and self-plagiarism constitutes an academic offence.

Clarisse Campos

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Resumo

As doenças pulmonares intersticiais são um grupo heterogéneo de doenças respiratórias agudas e crónicas, com diversas apresentações clínicas e desfechos. Um dos maiores desafios no diagnóstico e tratamento das doenças intersticiais pulmonares resulta das suas múltiplas etiologias e complexa fisiopatologia. Krebs von den Lungen-6 (KL-6), uma glicoproteína de elevado peso molecular, também conhecida como mucina humana 1 (MUC1), é predominantemente expressa através da regeneração de pneumócitos do tipo II e é, atualmente, utilizada na prática clínica japonesa como um dos principais biomarcadores séricos para o diagnóstico, avaliação de atividade da doença e previsão de resultados clínicos de vários tipos de doença pulmonar intersticial, incluindo a fibrose intersticial idiopática, a pneumonite de hipersensibilidade, a doença intersticial pulmonar associada a doenças do tecido conjuntivo, a sarcoidose pulmonar, a lesão pulmonar induzida por radiação e a doença pulmonar intersticial induzida por fármacos. Além disso, os níveis séricos de KL-6 ajudam no rastreio, na previsão da ocorrência de exacerbação aguda e na monitorização da resposta terapêutica em doentes com doença pulmonar intersticial. Os resultados de vários estudos apoiam a utilidade de incorporar a determinação dos valores séricos de KL-6 nas diretrizes clínicas, proporcionando uma ferramenta de estratificação do risco para a gestão personalizada das doenças intersticiais pulmonares e sublinhando a necessidade de esforços colaborativos para permitir a difusão da sua aplicação clínica internacionalmente.

Palavras-Chave: KL-6; biomarcador sérico; doença intersticial pulmonar; fibrose pulmonar idiopática; pneumonite de hipersensibilidade; doença intersticial pulmonar associada a doença do tecido conjuntivo.

Abstract

Interstitial lung diseases (ILDs) are a heterogeneous group of acute and chronic respiratory diseases with diverse clinical presentations and outcomes. One of the major challenges in diagnosing and managing ILDs arises from their multifarious aetiologies and intricate pathophysiology. Krebs von den Lungen-6 (KL-6), a high-molecular-weight glycoprotein also known as human mucin 1 (MUC1), is predominantly expressed by regenerating type II pneumocytes and is currently used in Japanese clinical practice as a leading serum biomarker for diagnosing, evaluating disease activity, and predicting the clinical outcomes of various ILD types, including idiopathic interstitial fibrosis, hypersensitivity pneumonitis, connective tissue disease-associated ILD, pulmonary sarcoidosis, radiation-induced lung injury, and drug-induced ILD. Moreover, serum KL-6 levels help in screening, predicting the occurrence of acute exacerbation, and monitoring therapeutic responses in ILD patients. The results from multiple studies support the usefulness of incorporating serum KL-6 into clinical guidelines and providing a risk stratification tool for the personalized management of ILDs, thereby stressing the need for collaborative efforts toward improving its clinical implementation internationally.

Keywords: KL-6; serum biomarker; interstitial lung disease; idiopathic pulmonary fibrosis; hypersensitivity pneumonitis; connective tissue disease-associated interstitial lung disease.

List of Abbreviations

AE-ILD: acute exacerbation of interstitial lung disease

BAL: bronchoalveolar lavage

bFGF: basic fibroblast growth factor

CLEIA: chemiluminescent enzyme immunoassay

COVID-19: coronavirus disease 2019

cHP: chronic hypersensitivity pneumonitis

CTD: connective tissue disease

CTD-ILD: connective tissue disease-associated interstitial lung disease

DIILD: drug-induced interstitial lung disease

DLCO: diffusing capacity of the lungs for carbon monoxide

DP: disease progression

EGFR-TKIs: epidermal growth factor receptor tyrosine kinase inhibitors

ELISA: enzyme-linked immunosorbent assay

FEV1: forced expiratory volume in one second

FVC: forced vital capacity

HP: hypersensitivity pneumonitis

HRCT: high-resolution computed tomography

Ig: immunoglobulin

IL: interleukin

ILDs: interstitial lung diseases

IIM: idiopathic inflammatory myopathies

IPF: idiopathic pulmonary fibrosis

KL-6: krebs von den lungen- 6

MDA5: melanoma differentiation-associated protein 5

MUC1: human mucin 1

NSCLC: non-small cell lung cancer

NSIP: non-specific interstitial pneumonia

PaO_2: partial pressure of oxygen

PDGF: platelet-derived growth factor

PFT: pulmonary function tests

pSS: primary sjogren's syndrome

RA: rheumatoid arthritis

RILI: radiation-induced lung injury

RP: radiation pneumonitis

SP: surfactant protein

SSc: systemic sclerosis

SSc-ILD: systemic sclerosis-associated interstitial lung disease

TGF-β: transforming growth factor-beta

TLC: total lung capacity

UIP: usual interstitial pneumonia

VEGF: vascular endothelial growth factor

VMRC-LCR: virginia mason research centre-lung cancer

Contents

Introduction

Interstitial lung diseases (ILDs) include a wide range of acute and chronic respiratory diseases of known and unknown aetiology that involve the pulmonary parenchyma, particularly the interstitial lung tissue, and alveoli. These conditions manifest with variable clinical, radiological, and respiratory functional repercussions due to inflammation and or fibrosis. Disease behaviour is heterogeneous in ILDs, which leads to different progression rhythms, responses to treatment, and impacts on an individual's quality of life. The clinical evaluation strives to pinpoint potential underlying causes and screen for features of systemic disease or environmental triggers. Occupational, recreational, and domestic exposures, radiation, and drugs can play a crucial role in the physiopathology of ILDs. When there is no identifiable underlying aetiology, they are defined as idiopathic (1–4).

The diagnosis of ILDs is complex and requires a multidisciplinary approach involving the integration of clinical, functional, radiological, and immunological data, as well as the analysis of bronchoalveolar lavage (BAL) and, at times, histological information. Indeed, numerous research studies indicate that the diagnostic accuracy and consensus among different observers are superior when there is a multidisciplinary team diagnosis, in contrast to relying solely on the individual components (5). Furthermore, most of these diseases are chronic and progressive, underscoring the importance of early diagnosis for initiating pharmacological and non-pharmacological therapeutic interventions aimed at modifying prognosis and improving the patients' quality of life (5,6).

Although tools like pulmonary function tests (PFTs), high-resolution chest computed tomography (HRCT), and, eventually, lung biopsies are remarkable for diagnostic purposes, they are not as effective as serial prognostic indicators. The influence of observer bias and the requirement for patient cooperation can account for some lack of sensitivity. Moreover, frequent imaging scans subject patients to higher radiation exposure, and obtaining repeated lung samples is impractical due to the invasive nature of the procedure (7).

Consequently, given the need for minimally invasive tools to aid in early diagnosis, response to therapy, and predicting prognosis, there has been a growing interest in serum biomarkers (6). In fact, serum biomarkers hold significant advantages, including being accessible, cost-effective, reproducible, and quickly reflecting modest changes, exhibiting sensitivity and specificity towards a certain disease, and being easy to perform (7).

Biomarkers can be divided and categorized by pathophysiology pathways. Those implicated in alveolar epithelial cell damage and dysfunction have garnered significant

attention, given the shared pathophysiological development in ILDs, specifically type II pneumocyte injury or remodelling. These biomarkers, including Krebs von den Lungen-6 (KL-6), surfactant proteins (SP)-A, SP-D, and Clara cell secretory protein-16, have emerged as promising candidates in this diagnostic landscape. In addition, other molecules involved in angiogenesis and damage of endothelium (interleukin 8 (IL-8), vascular endothelial growth factor (VEGF)), oxidative stress, matrix deposition and remodelling (matrix metalloproteinases, fibrocytes, heat shock protein 47), immune dysregulation and inflammation can also be potential biomarkers in serum, BAL, and lung tissue samples (8,9).

Out of all these biomarkers, KL-6, SP-A, and SP-D are the most investigated and currently available across Japanese clinical setting. KL-6 shows an increase in lung fibrosis and inflammation, while SP-D is related mainly to lung inflammation (6,7,10).

This narrative review aims to provide an overview of the current scientific evidence regarding the potential role of KL-6 for diagnostic, therapeutic, and prognostic purposes in ILDs.

Materials and Methods

Search strategy and selection criteria

References for this review were identified through searches of PubMed, ScienceDirect, and Scopus databases between September 21st, 2023 and March 30th, 2024 (preferentially for studies published within the last 15 years, but incorporating pivotal papers published earlier than 2000), in English, by use of the terms “KL-6”, "MUC1", "serum biomarker", "interstitial lung disease", "pulmonary fibrosis", "idiopathic pulmonary fibrosis”, “hypersensitivity pneumonitis", “collagen vascular disease-associated interstitial lung disease”, “radiotherapy pneumonitis”, “drug-induced interstitial lung disease”, "sarcoidosis", “pulmonary fibrosis in COVID-19”, “acute exacerbation”, “progressive pulmonary fibrosis” or a combination thereof. Articles considered for inclusion comprised meta-analyses, randomized studies, and case reports. Additionally, relevant references from the identified database search results were also included. Duplicate articles or those inaccessible were excluded.

Krebs von den Lungen (KL-6)

By immunizing a mouse with human lung adenocarcinoma VMRC-LCR (Virginia Mason Research Centre-Lung Cancer R) cells**,** a murine immunoglobulin (Ig) G1 monoclonal antibody was developed to target a protein with a sialylated sugar chain, designated KL-6 (11). KL-6 is a high-molecular-weight glycoprotein, also known as MUC1 (human mucin 1) and was first

introduced by Kohno *et al.* in 1988. The study described the elevation of serum KL-6 levels in interstitial pneumonia and a possible correlation to disease activity (12). This molecule is predominantly expressed in type II pneumocytes and bronchiolar epithelial cells, and its release is potentiated in the presence of inflammation, alveolar damage, or regeneration of these cells; increased permeability following alveolar-capillary barrier integrity loss might contribute to the release of KL-6 into the serum. Additionally, studies suggest that high levels of KL 6 in the lining fluid can promote fibrotic processes in ILDs exhibiting both chemotactic and anti-apoptotic effects stronger than those induced by PDGF (platelet-derived growth factor) bFGF (basic fibroblast growth factor) and TGF-β (transforming growth factor-beta) (11).

KL-6, originally proposed as a serum biomarker for various cancers, exhibited limited diagnostic potential compared to other tumour markers. Nevertheless, it was identified as a potential biomarker for non-malignant lung diseases. In 1992, investigations by Eidia Co., Ltd. in Tokyo, Japan, led to the development of an enzyme-linked immunosorbent assay (ELISA) for accurate KL-6 measurement in clinical samples. KL-6 was then approved as a diagnostic biomarker for ILDs in Japan in 1999. Further, a new chemiluminescent enzyme immunoassay (CLEIA) system was developed, capable of measuring serum KL-6 levels within an hour in standard Japanese clinical practice. Despite these advancements, this process is not yet widely available for clinical use in most countries. (6,10)

KL-6 levels are abnormally high in ILD patients, which rarely occurs in healthy individuals or those with other lung conditions. In fact, a KL-6 concentration of 500 U/mL serves as a meaningful threshold for distinguishing between patients with ILD and healthy individuals or patients with other lung diseases (10,13). However, variables like smoking, aging, renal function, and specific genetic factors, such as the rs4072037 gene variant, can influence KL-6 concentrations (14).

In prior investigations, an elevated KL-6 level has been linked to a significant decline in lung function, suggesting its potential as a valuable marker for evaluating the extent of ILD. Higher KL-6 levels (≥ 800 U/mL) were associated with lower lung function (measured by forced vital capacity (FVC), diffusing capacity of the lungs for carbon monoxide (DLCO), and total lung capacity (TLC)), and diminished exercise capacity, with greater desaturation and reduced six-minute walking distance (1,15–17).

Additionally, the same studies demonstrated a positive correlation between serum KL-6 levels and higher HRCT fibrosis scores in patients with ILD. Furthermore, individuals whose final diagnosis leading to death was progressive ILD exhibited extensive ground-glass opacity on

HRCT along with elevated KL-6 concentrations in serum, supporting once more the correlation between serum KL-6 levels and severity of ILDs (1,15–18).

These investigations suggest that applying higher serum KL-6 thresholds could serve as a valuable tool in pinpointing patients who might benefit from earlier treatment to forestall the progression of ILD. On the other hand, they also raise the possibility of basing the decision to perform HRCT in a patient with ILD on the presence of elevated KL-6 levels (15,17).

KL-6 and Idiopathic Pulmonary Fibrosis (IPF)

IPF is the predominant form of progressive ILD. It is a chronic, fibrosing interstitial pneumonia with unknown aetiology primarily affecting elderly male smokers and with a median survival of 3 to 5 years (19,20).

Studies investigating KL-6 levels in various ILDs demonstrated consistently higher serum KL-6 levels in IFP patients compared to healthy controls and individuals with other ILDs, such as sarcoidosis, hypersensitivity pneumonitis (HP), and connective tissue disease-associated interstitial lung disease. (CTD-ILD). Additionally, the positive correlation between KL-6 BAL and serum levels further supports its diagnostic relevance. In this study, neither environmental exposure nor smoking significantly affected serum KL-6 values, highlighting its specificity for IPF diagnosis. These findings collectively highlight KL-6 as a promising diagnostic tool for ILDs, particularly in distinguishing IPF from other conditions (21,22).

Despite the generally poor prognosis associated with IPF, the clinical trajectories of affected individuals exhibit considerable variability. Moreover, it is challenging to identify patients at high risk of disease progression, which can be defined as a decline in FVC and or DLCO, worsening symptoms, and an increase in fibrosis observed in HRCT scans. Therefore, serum biomarkers may present a solution in these cases. Serum baseline KL-6 levels seem to independently predict disease progression (DP) in IPF patients, with higher KL-6 levels noted in individuals experiencing DP compared to those with stable disease. Additionally, when KL-6 levels rise above 1000 U/mL, there is a clear association with increased mortality in IPF, suggesting its value for disease management (19,20).

Moreover, studies investigating the prognostic value of KL-6 in IPF revealed insightful findings. Elevated KL-6 levels were associated with lower FVC, forced expiratory volume in one second (FEV1), TLC, and DLCO in IPF patients, suggesting that there may be a relation between increased amounts of this glycoprotein and severity at onset. Additionally, KL-6 was investigated as a biomarker for progressive pulmonary fibrosis, focusing on identifying high-risk

patients. Elevated KL-6 expression levels in both BAL fluid and serum samples from progressive pulmonary fibrosis patients compared to non-progressive pulmonary fibrosis counterparts underscore its association with worsened prognosis and accelerated ILD deterioration. Serial monitoring of KL-6 levels over time reveals its potential in predicting disease trajectories in IPF and prompting consideration of additional therapies (21,23).

Serial evaluation of serum KL-6 in IPF patients over 24 months of nintedanib treatment revealed that most patients experienced a stabilization of lung function parameters and serum concentrations of KL-6. Patients whose KL-6 levels remained high despite two years of anti-fibrotic treatment experienced declining FVC and DLCO values over time, whereby repeated measurements of KL-6 might predict functional disease progression and response to anti-fibrotic therapeutic. Additionally, those with higher baseline levels of KL-6 have more severe fibrous destruction, thus limiting therapeutic efficacy and increasing chances for adverse outcomes, including even on-treatment mortality (KL-6 levels ≥3.5 ng/mL) (24,25).

KL-6 and Hypersensitivity Pneumonitis (HP)

HP is a complex interstitial lung disease characterized by an immunological response triggered by prolonged inhalation of various organic or chemical particles that occurs in individuals sensitized to specific environmental antigens, involving immune complex-mediated (type 3) and delayed (type 4) hypersensitivity reactions. Traditionally categorized into acute, sub-acute, and chronic forms, a more recent classification distinguishes between non-fibrotic or inflammatory HP and fibrotic HP based on clinical, radiological, and pathophysiological features (26,27).

In prior research, patients with fibrotic HP had consistently elevated serum KL-6 levels, highlighting its diagnostic potential (28,29).

Additionally, KL-6 concentrations could differentiate HP severity, with higher levels associated with decreased predicted lung function indexes such as DLCO and FEV1. These findings suggest that serum KL-6 testing could be a non-invasive method for assessing HP severity and progression. Furthermore, another study revealed that pigeon fanciers with early-stage acute symptoms exhibited elevated plasma KL-6 levels and IgG antibodies, indicating immune hypersensitivity. Among asymptomatic pigeon fanciers, KL-6 levels were comparable to normal, while those with early-stage acute HP exhibited higher KL-6 levels but still lower than the diagnosed HP cases. KL-6, indicative of alveolar remodelling, and IgG collectively demonstrated pathophysiological changes in individuals with early-stage acute HP.

Consequently, elevated KL-6 levels were proposed as a biomarker to identify pre-clinical individuals at risk of HP progression, even before formal diagnosis (28,29).

Another study investigated male former or non-smokers with chronic hypersensitivity pneumonitis (cHP) displaying radiological fibrotic involvement. Among these patients, environmental exposure in rural or agricultural settings and bird exposure were prevalent. Specific IgG antibodies were associated with higher BAL lymphocytosis and confirmed exposure to HP-related organic antigens. Moreover, a possible prognostic value of BAL KL-6 was also proposed, as its concentrations correlated with serum KL-6 levels and BAL lymphocytosis. Additionally, those with extensive HRCT evidence of ground-glass opacities and centrilobular nodules had the highest levels of KL-6 in BAL and serum, along with CD3+ and CD8+ predominance lymphocytosis in BAL. These findings underscore the potential utility of BAL KL-6 as a biomarker for disease management and prognostic conclusions, especially when combined with radiological findings (30).

KL-6 and Connective Tissue Disease-associated Interstitial Lung Disease (CTD-ILD)

ILD is a relevant manifestation in patients with connective tissue diseases (CTD), with approximately 15% of individuals experiencing both CTD and ILD. In patients diagnosed with CTDs exhibiting potential ILD manifestations, a notable elevation in serum KL-6 levels was observed. Patients suffering from Systemic Sclerosis (SSc), Idiopathic Myositis, and Polymyositis have a higher ILD prevalence, emphasizing the need for more frequent ILD screening in these individuals compared to Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus, and primary Sjögren's Syndrome (pSS) patients (31).

Additionally, there was a significant and positive correlation between CTD-ILD severity, assessed through chest HRCT, and serum KL-6 levels. Specific cut-off values for KL-6 were proposed according to ILD severity. Furthermore, lung function testing parameters demonstrated a significant negative correlation with serum KL-6 levels. The findings suggest that incorporating regular KL-6 measurements with periodic chest HRCT could constitute an optimal surveillance protocol for monitoring progression in CTD-ILD, especially in asymptomatic patients, where determining the ideal interval for HRCT scans and PFTs remains challenging (32–34).

Systemic Sclerosis (SSc)

Pulmonary hypertension and pulmonary fibrosis stand as leading contributors to the mortality associated with SSc. KL-6 may serve as a marker of epithelial damage and fibrotic processes in the lungs, reflecting the ongoing interplay between epithelial cells, fibroblasts, and

immune cells in systemic sclerosis-associated interstitial lung disease (SSc-ILD), with numerous studies consistently reporting elevated serum KL-6 levels, underscoring its utility as a diagnostic marker (4,35).

On the other hand, the challenge of accurately predicting SSc-ILD prognosis and the need to promptly identify patients with progressive fibrotic disease for timely intervention has received greater attention. Consistent negative associations with pulmonary function and positive correlations with radiological evidence of impairment or extensive lung fibrosis have been observed, with levels exceeding 1000 U/mL linked to increased mortality at a 5-year follow-up in SSc-ILD patients. Fluctuations in KL-6 levels correspond with disease flare-ups or improvements, while thresholds over 1273 U/mL are associated with end-stage SSc-ILD, those above 2000 U/mL in SSc patients undergoing treatment indicate poor therapeutic response, particularly to corticosteroids and cyclophosphamide. Additionally, investigations demonstrate that increased KL-6 levels can predict ILD progression and deterioration in pulmonary performance, underscoring the importance of monitoring KL-6 changes to start prompt therapeutic intervention and risk assessment in SSc-ILD. Also, optimal thresholds for KL-6 (≥ 1472 U/mL) predict a decline in DLCO (≥15%), which facilitates risk stratification and might offer a potential tool for identifying patients likely to benefit from intensified treatment (35–37).

Idiopathic Inflammatory Myopathies (IIM)

KL-6 has been associated with interstitial pneumonia in polymyositis and dermatomyositis; monitoring its levels might aid in screening early ILD changes (38,39).

Furthermore, elevated serum KL-6 concentrations in idiopathic myositis and dermatomyositis patients have emerged as indicative of the severity of ILD, disease activity, and lung involvement as reflected by HRCT fibrosis scores and decreased DLCO values, particularly in those with anti-melanoma differentiation-associated protein 5 (anti-MDA5) antibody positivity. Additionally, there is a decrease in KL-6 levels following disease control, and elevated KL-6 levels are linked to poorer outcomes and lower survival rates, suggesting its potential as a valuable prognostic indicator for risk stratification and treatment planning (38–40).

Moreover, patients with polymyositis-associated ILD exhibited the highest levels of KL-6 compared to other CTD-ILD patterns, suggesting that while the underlying CTD type may not influence KL-6 levels, patients with polymyositis are more likely to experience severe lung involvement (31).

Despite advances in combined immunosuppressive therapy, some patients face disease progression and adverse outcomes. Early screening of rapidly progressive ILD using biomarkers like KL-6 may allow for early intervention and aggressive management of these patients to mitigate disease progression and prevent fatal complications. KL-6 was measured before and after the initiation of combined immunosuppressive therapy, with a relevant increase in KL-6 levels during the first four weeks considered a marker of resistance to immunosuppressive treatment (38,41).

In antisynthetase syndrome-associated ILD, serum KL-6 levels above 644.71 U/mL were identified as an independent risk factor for progressive pulmonary fibrosis, suggesting the utility of KL-6 as a predictive marker for this outcome (42).

Rheumatoid Arthritis (RA)

KL-6 was elevated in rheumatoid arthritis-associated ILD (RA-ILD) patients, proving its diagnostic value. Furthermore, lung ultrasound B-lines, indicative of interstitial lung involvement, demonstrated a positive correlation with serum KL-6 levels. Combining lung ultrasound, KL-6 levels, and the assessment of respiratory symptoms as non-invasive and cost-effective measures presents an opportunity for early RA-ILD screening and guiding subsequent HRCT and PFT evaluations (43,44).

On the other hand, KL-6 exhibited a positive correlation with HRCT fibrosis scores and an inverse association with lung function and exercise capacity, strengthening the promise of the usefulness of KL-6 as a biomarker for discriminating ILD and assessing the disease extent in RA patients (44,45).

Notably, a high KL-6 level was an independent predictor of mortality in RA-ILD patients, particularly in the Usual Interstitial Pneumonia (UIP) pattern. However, KL-6 did not emerge as a significant prognostic factor in the non-UIP group, possibly indicating varying degrees of alveolar epithelial damage between UIP and non-UIP patterns (45).

Primary Sjogren’s Syndrome (pSS)

The possibility of evaluating the diagnostic utility of serum KL-6 in patients with primary Sjögren's syndrome (pSS) and its association with ILD has been investigated. Those with mild ILD in chest HRCT scan and normal chest X-ray had higher serum KL-6 levels, suggesting its value for early detection of pulmonary damage. While most patients with pulmonary involvement are asymptomatic, they may exhibit functional impairment, reflected in reduced DLCO. The study emphasizes the importance of KL-6 as a valuable biomarker in screening mild ILD in pSS patients (46).

Patients with high KL-6 serum levels exhibited poorer lung function, exercise capacity, and higher mortality rates correlating with the severity of pSS-ILD. Disease duration and KL-6 levels were the key parameters associated with pulmonary involvement in pSS patients. Moreover, the elevation of KL-6 levels was considered an independent factor for increased 10-year mortality when evaluating the potential prognostic significance of serum biomarkers in pSS-ILD patients (47–49).

KL-6 and Pulmonary Sarcoidosis

Sarcoidosis is a chronic and multisystemic inflammatory condition characterized by non-caseating granulomas, majorly affecting the lungs and lymphatic nodes. This idiopathic condition implies an abnormal immune response connected with T lymphocyte and macrophage activation and migration, leading to organ dysfunction. The cause of sarcoidosis is unknown, but it may occur due to genetic susceptibility and environmental factors. Sarcoidosis can present in many ways, from asymptomatic patients to severe organ involvement. In the appropriate clinical context, CD4+ T-helper cells within involved tissues and an increased CD4+/CD8+ T cells ratio in BAL support the diagnosis of sarcoidosis. Despite this, histological examination remains an essential requirement. Thus, finding diagnostic biomarkers in the serum or BAL of sarcoidosis patients might help as non-invasive diagnostic clues (6).

There was a significant correlation between serum KL-6 levels and the number of total cells, lymphocytes, and CD4+T lymphocytes in BAL, indicating that it might reflect active lymphocytic alveolitis. Patients with pulmonary infiltration had a significantly higher incidence of pulmonary involvement when compared to those without parenchymal infiltration, demonstrated by higher KL-6 levels. For this reason, KL-6 levels at disease onset were proposed as a good marker for evaluating the severity of parenchymal infiltration and epithelial cell damage in pulmonary sarcoidosis. These findings show that KL-6 could serve as a valuable tool for understanding these inflammation-mediated events, as well as in assessing the disease severity and offering prognostic value in sarcoidosis (50,51).

Moreover, the unpredictable course of the disease underlines the practical relevance of serum biomarker detection in monitoring sarcoidosis during follow-up. KL-6 emerged as an accurate indicator of fibrotic lung involvement, correlating with decreased FVC, DLCO, partial oxygen pressure (PaO_2), and functional impairment (22,52).

KL-6 and Radiation-Induced Lung Injury (RILI)

RILI comprises two distinct phases: an initial stage referred to as Radiation Pneumonitis (RP), characterized by acute inflammation following radiation exposure; and Radiation Fibrosis, a late phase that arises from prolonged pulmonary damage. Combination treatment (radiation therapy combined with antineoplastic agents) may be synergistic in lung toxicity (radiation recall pneumonitis). RILI is a diagnosis of exclusion, based on clinical and radiographic information (53,54).

Previous studies explored the diagnostic utility of KL-6 in RP following radiotherapy for lung tumours and breast-conservation surgery, shedding light on its potential as a diagnostic marker in these settings. Positive correlations between interstitial pneumonitis changes in HRCT scans and elevated serum KL-6 values before stereotactic body radiotherapy for lung tumours were documented. High KL-6 levels were associated with the onset of severe RP, suggesting its potential as an indicator for RP diagnosis, particularly in patients without clear interstitial pneumonitis, and the application of KL-6 in predicting RP after stereotactic irradiation of lung tumours was established. KL-6 serum levels increased significantly one to two months before RP symptoms manifested, and the ratio of this increase was a predictive factor for RP occurrence. Similarly, in research focusing on radiotherapy after breast-conservation surgery, serum KL-6 levels increased in patients who developed RP post-radiotherapy. Thus, monitoring KL-6 levels before and after radiotherapy is recommended to facilitate the RP diagnosis (55–57).

KL-6 and Drug-Induced Interstitial Lung Disease (DIILD)

DIILD represents a heterogeneous group of adverse drug reactions, ranging from mild to severe and life-threatening conditions. More than 400 causative drugs have been reported, including disease-modifying antirheumatic drugs, antiarrhythmics, and antimicrobial and antineoplastic agents. The mechanisms of DIILD could be due to the direct toxicity of the drug, the release of various mediators leading to lung injury, or oxidant/antioxidant imbalance. The lung injury can manifest as alveolitis, pulmonary oedema, and abnormal fibrotic repair reaction. The clinical, laboratory, radiological, and histological manifestations of DIILD are variable, even with the same causative drug suggesting a complex pathophysiology involving genetic or environmental factors. DIILD is a diagnosis of exclusion, relying on clinical suspicion, and prior exposure to a drug known for lung toxicity (54,58).

The possibility of applying KL-6 levels to diagnose and predict the severity of DIILD in lung cancer patients undergoing diverse therapeutic agents has been researched. There is a

significantly higher median serum KL-6 level in patients with DIILD compared to those without, reinforcing its potential as a diagnostic biomarker. Additionally, high KL-6 levels can independently predict severe DIILD, indicating that serum KL-6 levels at baseline may help predict prognosis in lung cancer patients, according to possible relationships with concomitant diseases, tumour burden, and treatment strategy (59).

Furthermore, there were significant advancements in investigating the mechanisms of ILD caused by EGFR-TKIs and using serum KL-6 levels to predict the patient outcome and treatment plans for NSCLC. Baseline pulmonary fibrosis was an important risk factor associated with EGFR-TKIs-induced ILD. The ratio of KL-6 levels at ILD onset to baseline proved effective in differentiating life-threatening ILD, suggesting its potential as a marker of disease severity. It is also worth mentioning that monitoring serum KL-6 levels was proposed as a more rapid, cost-effective, and accessible method than HRCT scans for evaluating NSCLC patients treated with EGFR-TKIs and timely detection and management of ILD (60). On the same note, another research confirmed the feasibility of incorporating KL-6 assessment into diagnostic algorithms aimed at early recognition and treatment of ILDs among cancer patients treated with immune checkpoint inhibitors. For lung cancer patients, immune checkpoint inhibitor-related pneumonitis occurred earlier than it did in other cancers, and its onset was not influenced by a history of radiation exposure. Conversely, however, higher KL-6 levels were correlated with onset in non-lung cancer patients but not lung cancer patients (60,61).

KL-6 and COVID-19 (coronavirus disease 2019)

Compared to healthy adults, KL-6 levels are usually higher in COVID-19 patients, but still significantly lower compared to ILD patients. Severe or critical COVID-19 may predispose the patient to the development of lung fibrotic disease following diffuse alveolar damage. Serum KL-6 levels should be carefully monitored because an increase in this glycoprotein might indicate further progression towards a fibrotic process during COVID-19 (62,63).

The study by Yoshifuji *et al.* described the case of a suspected COVID-19 vaccine-associated interstitial lung disease. This condition emerged in a patient who suffered from dyspnoea and hypoxemia after receiving the second dose of the COVID-19 vaccine. The patient did not have other drug triggers or pulmonary disease history except for mild emphysema and chronic heart failure. The authors considered vaccine-induced pneumonia as the most likely diagnosis, as they ruled out other potential causes of respiratory failure, such as bacterial and viral pneumonia, COVID-19, CTD, and acute heart failure. In this case, laboratory findings of particular interest were KL-6 levels ≥800 U/mL. Chest HRCT findings included extensive ground

glass opacities, mild interlobar septal wall involvement, and diffuse bronchial wall thickening (64).

KL-6 and Acute Exacerbation of Interstitial Lung Disease (AE-ILD)

In the event of an acute exacerbation of ILD (AE-ILD), KL-6 levels further increase (15,23,47,65). This heightened KL-6 level during AE-ILD emphasizes its potential as a dynamic biomarker for tracking disease activity, predicting the occurrence, and evaluating the severity of AE-ILD, which represents the most common cause of death in ILD patients. Additionally, a rapid increase in KL-6 levels serves as an indicator to distinguish progressive ILD from chronic ILD (15).

These studies focused on whether baseline serum KL-6 concentrations can predict acute exacerbation risk in IPF and CTD-ILD patients. Regarding IPF, results showed that patients who experienced AE-ILD had significantly higher baseline serum KL-6 levels when compared to those who were free from AE-ILD. Multivariate analysis demonstrated that decreased vital capacity and baseline serum KL-6 levels (as a continuous value and with a cutoff of 1300 U/mL) were independent risk factors for developing AE-ILD. This finding is notable as KL-6 is the first biomarker to predict AE risk in IPF patients. Despite the high sensitivity of KL-6 (92%), the study acknowledged its low specificity (61%), resulting in a high rate of false positive results at 39%. It implies that raised KL-6 can predict a high AE-IPF risk, though normal levels do not necessarily mean low risk (23). Moreover, other research noted that KL-6 levels above 1000 IU/L can predict 3-month mortality in IPF patients diagnosed with AE, even though some studies don't correlate higher levels of KL-6 at the time of exacerbation with a poorer prognosis (66). Additionally, elevated KL-6 levels were significantly associated with the occurrence and frequency of AE among patients with CTD-ILD, such as RA-ILD and pSS-ILD (47,65).

Research by Geun Choi *et al.* linked alterations in serum biomarkers with mortality in patients experiencing AE-ILD during hospitalization. Baseline C-reactive protein levels, the partial pressure of oxygen to the fraction of inspired oxygen, and changes in KL-6 were independent prognostic factors for in-hospital mortality among individuals with ILD during AE. Specifically, an increase in KL-6 levels above 10% over one week emerged as a significant discriminator for poor prognosis (67).

Research regarding the relationship between preoperative KL-6 levels and AE occurrence in lung cancer patients undergoing lung resection, suggested a close association between high preoperative KL-6 values and AE development, particularly in patients with interstitial pneumonia. Notably, patients undergoing partial lung resection showed no AE cases,

suggesting a potential risk reduction with lesser operative insult. Overall, the study indicates that AE can occur in lung cancer patients with non-specific interstitial pneumonia (NSIP) patterns, especially those with fibrotic NSIP patterns. KL-6 emerges as a potential prognostic factor for post-operative AE, with partial resection considered an option to prevent AE in patients with high KL-6 values (68).

Conclusion

Studies consistently indicate that serum KL-6 levels are high in ILD patients, demonstrating its utility for detecting ILD and correlating with disease severity, deterioration of lung function parameters, and adverse clinical outcomes. KL-6, specifically, points to pulmonary involvement by reflecting alveolar epithelial damage and fibrotic processes, which allows monitoring of the progression of the disease and the response to treatment over time. The measurement of KL-6 is accessible, rapid, cost-effective, reproducible, and easy to perform and can also be used as a serial prognostic indicator. However, the literature has some drawbacks and gaps regarding KL-6's potential use which include different ethnic populations in studies that limit the generalizability of findings as comparisons are not valid. There is also a need for standardization of the assay methods and reference ranges to make sure that clinical value is validated. More prospective longitudinal investigations are required to establish a relationship between KL-6 levels (as a reliable biomarker) and progressive pulmonary fibrosis. For this reason, current guidelines stress the need for validated serum biomarkers that could help identify people at risk of progressive pulmonary fibrosis (69); KL-6 is promising in this sense since it is a non-invasive way of stratifying ILD patients into different risk levels and thus anticipate therapeutic interventions.

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