BMC Pulmonary Medicine

RESEARCH

Open Access

Evaluating the diagnostic and prognostic utility of serial KL-6 measurements in connective tissue disease patients at risk for interstitial lung disease: correlations with pulmonary function tests and high-resolution computed tomography

Jorge Álvarez Troncoso[1*], Óscar Porto Fuentes[2], María Fernández Velilla[3], Luis Gómez Carrera[4], Clara Soto Abánades[1], Elena Martínez Robles[1], Raquel Sorriguieta Torre[1] and Juan José Ríos Blanco[1]

Abstract

Background Interstitial lung diseases associated with connective tissue diseases (CTD-ILD) necessitate reliable biomarkers for effective management. This study assesses the utility of serial Krebs von den Lungen-6 (KL-6) measurements in predicting disease activity and progression in CTD-ILD patients.

Methods In a prospective cohort study at a tertiary care center, 50 patients with CTD at risk of or diagnosed with ILD were enrolled. KL-6 levels and pulmonary function tests (PFTs) were measured at baseline, 6, and 12 months, alongside high-resolution computed tomography (HRCT).

Results Initial KL-6 levels were inversely correlated with PFTs, with mean values starting at 504.96 U/mL (SD ± 508.46), escalating to 739.42 U/mL (SD ± 612.75) at 6 months, and peaking at 1150.27 U/mL (SD ± 1106.70) by 12 months, reflecting disease progression. Higher KL-6 levels were consistently linked with declines in Forced Vital Capacity (FVC) ($p = 0.019$) and Diffusing Capacity for Carbon Monoxide (DLCO) ($p < 0.001$). Radiologically, increased KL-6 correlated with subpleural thickening ($p = 0.003$), septal thickening ($p = 0.036$), ground-glass opacities ($p = 0.018$), and other signs of advanced ILD. Sensitivity and specificity of KL-6 for detecting ILD were 86.7% and 71.4%, respectively, at a ≥ 400 U/mL threshold, improving at higher thresholds. Over the study period, patients with elevated KL-6 levels demonstrated more pronounced radiological and functional deterioration.

Conclusion Serial KL-6 measurements effectively reflect disease activity and progression in CTD-ILD, with strong correlations to functional and radiological outcomes. These findings support the use of KL-6 as a valuable biomarker in the routine clinical management of these complex disorders. Our study demonstrates the significant predictive value of KL-6 for both the diagnosis and monitoring of CTD-ILD, suggesting its integration into clinical practice can enhance patient care and treatment strategies.

*Correspondence:
Jorge Álvarez Troncoso
jorge.alvarez.troncoso@gmail.com
Full list of author information is available at the end of the article

Keywords KL6, Interstitial lung disease, Autoimmune diseases, Computed tomography

Introduction

Interstitial lung diseases (ILDs) are a heterogeneous group of pulmonary disorders characterized by progressive fibrosis and inflammation of the lung parenchyma. This group encompasses a broad spectrum of etiologies, ranging from environmental exposures to systemic diseases [1–3]. Connective tissue disease-associated interstitial lung diseases (CTD-ILDs) represent a notable subset of these conditions, where pulmonary manifestations are intricately linked with systemic autoimmune diseases such as systemic sclerosis, rheumatoid arthritis, and mixed connective tissue disease [4, 5]. In these patients, the lung involvement often serves as a significant determinant of morbidity and mortality. The clinical course of CTD-ILD is highly variable, influenced by the specific CTD involved, the extent of lung damage, and the responsiveness to therapy [5–7]. Recent studies have highlighted the variability in disease progression and patient-reported outcomes in fibrotic ILDs, including CTD-ILDs, emphasizing the need for effective biomarkers to guide treatment and predict outcomes [8, 9].

Traditional diagnostic and monitoring techniques, including clinical assessment, pulmonary function tests (PFTs), and high-resolution computed tomography (HRCT), often fall short in precisely delineating disease activity and predicting outcomes due to the complex nature of CTD-ILD [5, 7, 10]. Moreover, the integration of innovative diagnostic tools such as the International Classification of Functioning, Disability, and Health (ICF) has been suggested to enhance clinical assessments in ILD patients [8]. Amid these challenges, Krebs von den Lungen-6 (KL-6), a mucin-like high-molecular-weight glycoprotein predominantly expressed by type II alveolar cells and bronchiolar epithelial cells, has gained prominence as a potential biomarker in the management of ILDs [10–12]. Elevated serum levels of KL-6 are indicative of increased epithelial cell turnover and damage, features that are prominent in the pathogenesis of ILDs. Studies have consistently shown that high levels of KL-6 are associated with disease activity in various forms of ILD, including idiopathic pulmonary fibrosis and CTD-ILD, suggesting its role in both diagnosis and disease monitoring [11, 13]. Furthermore, KL-6 has been linked to the progression of fibrotic changes in ILDs, adding a layer of complexity to patient management and highlighting its potential as a marker for therapeutic response [8].

However, despite the growing body of literature supporting the utility of KL-6, significant gaps remain in our understanding. The dynamic changes of KL-6 over the course of the disease, its correlation with morphological changes on HRCT, and its relationship with pulmonary function decline are not fully elucidated [11, 14]. Furthermore, while KL-6 appears to correlate with disease severity and progression, its utility in predicting therapeutic responses and long-term patient outcomes has not been robustly explored. Questions also persist regarding the optimal thresholds for KL-6 levels in differentiating disease states and the impact of underlying autoimmune conditions on its levels [15–17].

This study aims to evaluate the utility of serial KL-6 measurements in patients with CTD-ILD, investigating how changes in KL-6 levels correlate with alterations in pulmonary function tests, HRCT findings, and overall clinical progression. By integrating longitudinal clinical data, this research seeks to validate and potentially expand the prognostic and diagnostic capabilities of KL-6, with the ultimate goal of enhancing the clinical management of patients with CTD-ILD. The findings from this study could also provide insights into the broader implications of using biomarkers like KL-6 in routine clinical practice, paving the way for more personalized and effective therapeutic strategies in managing these complex disorders [8].

Methods

Study design and setting

This prospective cohort study was conducted at the Systemic Autoimmune Diseases Unit within the Internal Medicine Department of a tertiary care center. The study period extended from March 2023 to March 2024. The study aimed to evaluate the diagnostic performance of KL-6 in detecting ILD in patients with CTD and its correlation with PFTs and HRCT findings. This study was approved by the Ethics Commission of the Hospital Universitario La Paz (PI-5929) and complied with the Declaration of Helsinki.

Participants

Fifty consecutive patients with CTD at risk of developing ILD, with or without established ILD, were enrolled from the Systemic Autoimmune Diseases Unit within the Internal Medicine Department of a tertiary care center. Inclusion criteria required patients to fulfill recent classificatory criteria for a confirmed diagnosis of CTD based on clinical and serological parameters. All participants had KL-6 levels PFTs, and high-resolution computed

tomography (HRCT) performed within the last year. The presence or absence of ILD was defined by radiological criteria on HRCT. Exclusion criteria included a history of lung transplantation, active malignancy, pregnancy, or being under the age of 18.

Data collection

Baseline demographic information, medical background, and immune system data were documented. The levels of KL-6 in the blood serum were assessed when patients first visited, after six months for 19 patients, and after twelve months for 11 patients. Pulmonary function tests were carried out at baseline and during follow-up (among 6 to 12 months) for all patients. Additionally, HRCT testing was conducted on all patients in the previous year.

KL-6 Measurement

KL-6 levels were measured through a standardized enzyme-linked immunosorbent assay using monoclonal antibodies that are specific to the KL-6 antigen. This assay is specifically designed to detect elevated levels of KL-6, a mucin-like glycoprotein found in the serum of patients with ILDs, with high specificity and sensitivity[14, 18, 19].

Blood samples were collected from all participants at their initial visit, and at 6 and 12 months for follow-up assessments. The concentration of KL-6 is reported in units per milliliter (U/mL), with typical diagnostic thresholds established based on normative data and prior research in ILD populations.

Pulmonary function tests and HRCT

PFTs included measurements of Forced Vital Capacity (FVC), Forced Expiratory Volume in One Second (FEV1), Diffusing Capacity for Carbon Monoxide (DLCO) and Total Lung Capacity (TLC). In our study, HRCT was employed as the gold standard for diagnosing CTD-ILD. HRCT scans were performed at baseline and analyzed by experienced thoracic radiologists who were blinded to clinical and serological data.

Statistical analysis

Descriptive statistics summarized the demographic and clinical characteristics of the participants. The relationship between KL-6 levels, PFT results, and HRCT findings was analyzed using Pearson's correlation for continuous variables and Spearman's rank correlation for ordinal or non-normally distributed variables. Multivariable logistic regression analyses were performed to adjust for confounders such as age and sex, and to examine the predictive value of KL-6 for ILD diagnosis. Repeated measures analyses were used to assess changes over time in KL-6 levels and their relationship with PFTs. Statistical significance was set at a p-value of less than 0.05. Data analysis was conducted using Wizard Pro 2 software, version 2.0.16 (267). Figures were created with BioRender Poster Builder.

Results

Demographics and clinical characteristics

The study involved 50 patients diagnosed with CTD-ILD, with a majority being female (72%). The average age was 60.56 years (SD ± 14.99). Idiopathic inflammatory myopathies (IIM) were the most common CTD, affecting 46% of the patients (Table 1). In terms of immunological markers, myositis specific antibodies (MSA) tested positive in 48% of patients and Ro52 antibody in 28%.

KL-6 Serum levels

KL-6 serum levels varied across three time points: initial (KL6-1) levels were 504.96 U/mL (SD ± 508.46), at 6 months (KL6-2) they increased to 739.42 U/mL (SD ± 612.75), and by 12 months (KL6-3), they further escalated to 1150.27 U/mL (SD ± 1106.70) (Table 2).

Pulmonary Function Tests (PFTs)

Baseline pulmonary function tests (PFT-1) yielded the following measurements (mean % ± SD): FVC at 83.55% ± 19.25 of predicted, FEV1 at 82.16% ± 18.19, FEV1/FVC ratio at 97.26% ± 10.48, DLCO at 76.56% ± 18.84, and TLC at 80.81% ± 19.39.

Subsequent PFTs demonstrated overall stability ($p > 0.005$) across the entire cohort: FVC was 86.08% ± 19.88, FEV1 at

Table 1 Demographics and clinical characteristics

Demographics	
Female sex (%)	72.00%
Age (mean ± SD)	60.56 ± 14.99
Diseases (%)	
Idiopathic inflammatory myopathies	46.00%
Sarcoidosis	16.00%
Systemic sclerosis	10.00%
Interstitial Pneumonia with Autoimmune Features	6.00%
Sjögren syndrome	4.00%
ANCA vasculitis	2.00%
Systemic Lupus Erythematosus	2.00%
Miscellaneous	14.00%
Autoantibodies (%)	
Myositis specific antibodies (MSA)	46.00%
Ro52	28.00%
Systemic sclerosis antibodies (Scl70, centromere)	10.00%

Table 2 KL6, PFTs and HRCTs

KL6 values (mean ± SD)	
KL6-1 (baseline)	504.96 ± 508.46
KL6-2 (follow-up)	739.42 ± 612.75
KL6-3 (follow-up)	1150.27 ± 1106.70
PFTs at baseline (mean % ± SD)	
FVC-1	83.55 ± 19.25
FEV1-1	82.16 ± 18.19
FEV1/FVC-1	97.26 ± 10.48
DLCO-1	76.56 ± 18.84
TLC-1	80.81 ± 19.39
PFTs at follow-up (mean % ± SD)	
FVC-2	86.08 ± 19.88
FEV1-2	84.69 ± 19.08
FEV1/FVC-2	96.44 ± 12.01
DLCO-2	77.62 ± 22.61
TLC-2	82.78 ± 19.18
Interstitial lung disease (ILD) by HRCT (%)	30.00%
Radiological Findings at HRCT (%)	
Micronodules	50.00
Bronchiectasis	39.58
Granulomas	33.33
Ground glass opacity	27.08
Subpleural thickening	27.08
Septal thickening	27.08
Air trapping	20.83
Atelectasis	16.67
Thoracic lymphadenopathy	14.58
Fibroscarring tracts	14.58
Pericardial effusion	8.33
Esophageal dilatation	4.17
Pleural effusion	0.00

84.69% ± 19.08, FEV1/FVC ratio at 96.44% ± 12.01, DLCO at 77.62% ± 22.61, and TLC at 82.78% ± 19.18. Conversely, follow-up PFTs in the subgroup of patients with a second measurement of KL6 (KL6-2) indicated a numerical decline: FVC at 78.83% ± 22.25, FEV1 at 81.33% ± 20.53, FEV1/FVC ratio at 98.72% ± 13.97, DLCO at 68.77% ± 22.18, and TLC at 77.31% ± 20.95.

Radiological findings

HRCT scans were performed on all 50 patients. From these scans, 15 patients, representing 30% of the cohort, were diagnosed with CTD-ILD. Additionally, radiological findings showed that 50% of patients had micronodules, 33.33% had granulomas, and 39.58% exhibited bronchiectasis (Table 1). Subpleural thickening and septal thickening were each identified in 27.08% of the cases. Notably, there were no instances of pleural effusion, but pericardial effusion was present in 8.33% of the patients. Other findings included esophageal dilation in 4.17% of patients and air trapping observed in 20.83%. ILD patterns were classified as NSIP (40%), UIP (26.67%), OP (13.33%), LIP (6.67%), and mixed patterns (13.33%). Inflammatory findings were present in 66.67% of CTD-ILD patients, while 33.33% had fibrotic changes. ILD severity, defined as greater than 20% involvement on HRCT, was observed in 26.67% of patients.

Linear regression findings

KL6 levels demonstrated significant increases at each subsequent measurement, with the initial KL6 (KL6-1) averaging 504.96 (± 508.46) U/mL, increasing to 739.42 (± 612.75) U/mL by the second measurement (KL6-2), and reaching 1150.27 (± 1106.70) U/mL by the third (KL6-3), with all changes statistically significant ($p < 0.001$).

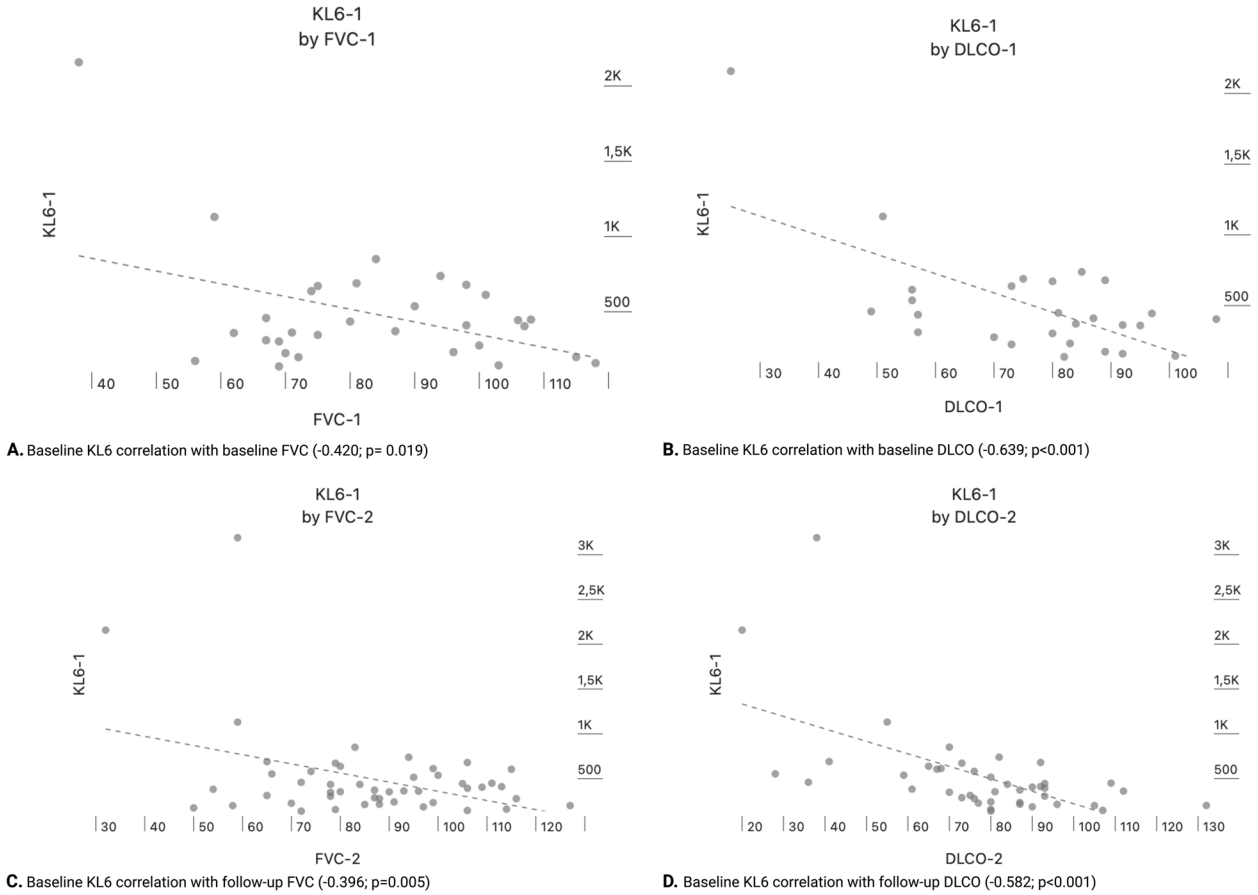
Baseline KL6 levels negatively correlated with initial pulmonary function measures: FVC ($p = 0.019$), FEV1 ($p = 0.049$), DLCO ($p < 0.001$), and KCO ($p = 0.023$). These negative correlations persisted into follow-up measurements, indicating a consistent relationship between rising KL6 levels and declining pulmonary function over time (Fig. 1).

Additionally, KL6 levels at baseline positively correlated with subpleural thickening ($p = 0.003$), septal thickening ($p = 0.036$), and esophageal dilation ($p = 0.016$). KL6-2 showed positive correlations with further radiological findings, including subpleural thickening ($p = 0.023$), septal thickening ($p = 0.009$), ground-glass opacities ($p = 0.018$), bronchiectasis ($p = 0.035$), and esophageal dilation ($p = 0.029$). Similarly, KL6-3 correlated positively with subpleural thickening ($p < 0.001$), septal thickening ($p = 0.028$), ground-glass opacities ($p = 0.028$), and esophageal dilation ($p = 0.024$).

Fibrotic changes on HRCT correlated with higher KL6-1 levels ($p < 0.001$) and KL6-2 levels ($p = 0.009$), and lower DLCO-1 ($p = 0.023$) and DLCO-2 ($p = 0.006$) values.

Analysis of the relationship between PFTs such as FVC, FEV1, DLCO and TLC and the diagnosis of ILD showed no significant correlations at baseline, with FVC-1 ($p = 0.657$), FEV1-1 ($p = 0.492$), DLCO-1 ($p = 0.197$), and TLC-1 ($p = 0.555$) not linked to the presence of ILD. Similarly, in the follow-up measurements, FVC-2 ($p = 0.340$) and FEV1-2 ($p = 0.576$) showed no correlations with ILD. However, negative correlations were observed at follow-up for DLCO-2 ($p = 0.006$) and TLC-2 ($p = 0.016$), suggesting that these follow-up PFTs may have predictive value for ILD.

Sequential KL-6 measurements demonstrate a marked distinction between patients with and without ILD. Initially, the mean KL-6 level in patients without ILD was considerably lower than that in ILD patients. This difference was amplified at both the six-month and one-year marks, with ILD patients showing progressive increases in KL-6 levels (Fig. 2).



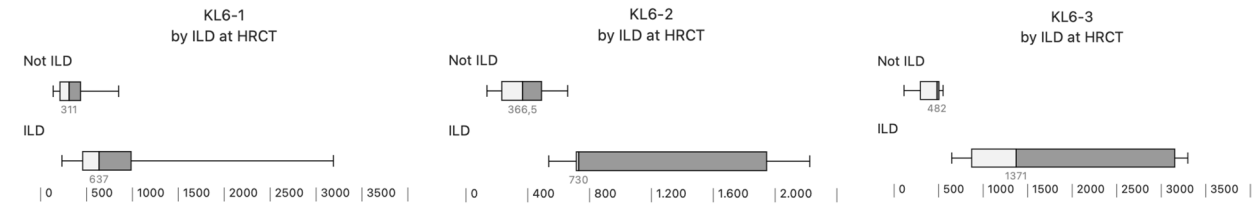
A. Baseline KL6 correlation with baseline FVC (-0.420; p= 0.019)

B. Baseline KL6 correlation with baseline DLCO (-0.639; p<0.001)

C. Baseline KL6 correlation with follow-up FVC (-0.396; p=0.005)

D. Baseline KL6 correlation with follow-up DLCO (-0.582; p<0.001)

Fig. 1 Correlations matrix



A. Baseline KL6

B. Follow-up KL6 (6 months)

C. Follow-up KL6 (12 months)

Fig. 2 Evolution of KL6 at follow-up, cut-offs and correlation with ILD

KL6 levels at baseline were higher in the NSIP pattern than in the UIP pattern (1330.17 vs 709.25 U/mL; $p=0.004$). However, KL6 levels at follow-up tended to decrease in the NSIP pattern (-321 U/mL) and increase in the UIP pattern (+348.67 U/mL).

Area under the curve analysis

The initial KL-6 had an AUC of 0.859, indicating a moderate predictive value for ILD diagnosis. At the follow-up, the AUC for KL6 increased to 0.978, showing a high predictive value for ILD. However, the combined AUC for FVC and DLCO at the initial visit was only 0.676 based on observed correlations, suggesting a lower predictive value compared to KL6 alone. Additionally, the AUC for FVC and DLCO at follow-up was 0.796, also indicating moderate predictive value. When combined with DLCO at baseline, there was a marginal improvement in the AUC for KL6 to 0.865 which signifies a slight enhancement in its predictive value for ILD diagnosis (Fig. 3).

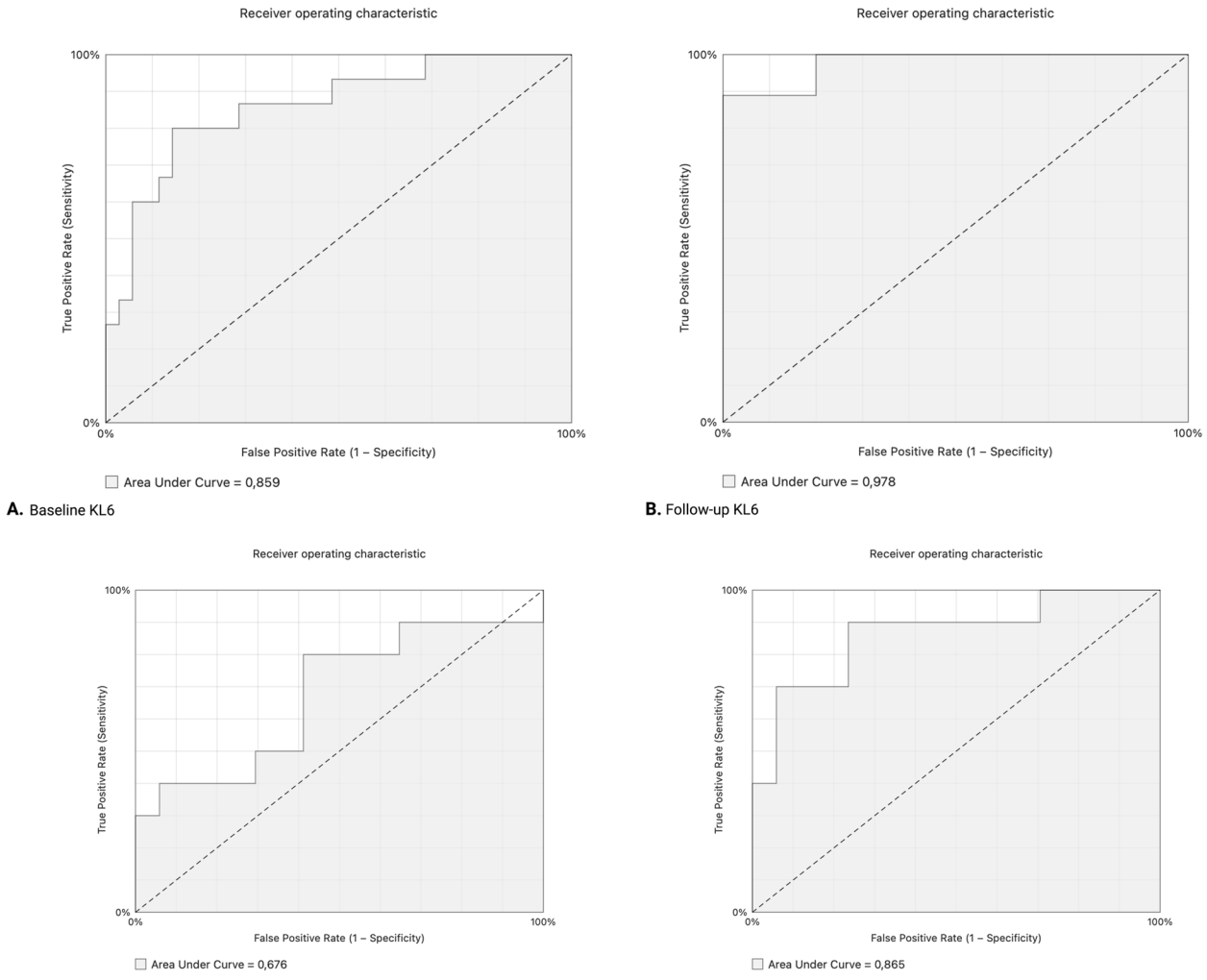


Fig. 3 Area Under the Curve for ILD diagnosis

A KL6 level at baseline of ≥ 400 UI/ml showed a sensitivity of 86.7%, a specificity of 71.4% and positive predictive value (PPV) of 56.5%, whereas a KL6 level of ≥ 500 UI/ml exhibited a sensitivity of 73.3%, a specificity of 85.7% and a PPV of 68.8%. For the threshold of KL6 ≥ 600 UI/ml, the sensitivity was found to be 60.0%, the specificity of 91.4% and the PPV 75.0%.

Discussion

KL6 Utility in CTD-ILD

The role of KL-6, a mucin-like high-molecular-weight glycoprotein, has been increasingly recognized in the management of ILD, particularly those associated with CTD [8, 11, 14, 20]. Our study underscores the potential of serial KL-6 measurements as a valuable biomarker in both diagnosing and monitoring the progression of CTD-ILDs. Elevated KL-6 levels were consistently associated with worsening pulmonary function, affirming its utility in reflecting ongoing epithelial damage and disease activity. Furthermore, the integration of biomarkers like KL-6 into the management of CTD-ILD represents a critical stride towards precision medicine in pulmonary care. As noted in recent literature, ILDs associated with CTD can present diverse responses to conventional treatments, necessitating more personalized therapeutic strategies [4, 7, 8]. This personalized approach not only has the potential to improve efficacy and reduce treatment-related toxicities but also underscores the importance of biomarker-driven decision-making in chronic diseases. In light of these considerations, this study's findings could significantly shift the paradigm in the diagnosis, monitoring, and management of CTD-ILD, providing a foundation for future research into other novel biomarkers and their integration into clinical protocols.

KL6 correlation with PFTs and HRCT

Our findings show that initial KL-6 levels negatively correlate with pulmonary function measures such as FVC and DLCO, aligning with previous studies that suggest a relationship between higher KL-6 levels and reduced lung function [14, 21]. Initial PFTs showed suboptimal correlation, while subsequent PFTs were found to have a stronger association with the presence of ILD. This indicates that KL-6 could provide supplementary diagnostic insight not captured by PFTs, especially in the early stages of the disease when functional impairment is less apparent. The substantial increase in AUC for KL6 from 0.859 at the initial visit to 0.978 at follow-up demonstrates its reliability in predicting ILD, indicating the potential of KL6 as a powerful tool for early detection and monitoring of ILD progression. It is evident that KL6 outperforms the combined AUC for FVC and DLCO, particularly at the initial visit where the combined AUC is relatively low at 0.676. The sensitivity and specificity of different threshold levels of KL6 further support its utility as a diagnostic biomarker for ILD. The high sensitivity at the 400 UI/ml threshold indicates that KL6 can effectively identify a majority of ILD cases with a relatively low false positive rate. As the threshold increases, so does specificity, reducing false positives but affecting sensitivity. These findings are consistent with prior studies that demonstrated the prognostic value of KL-6 in ILD [11, 13]. In summary, these findings collectively highlight the superior predictive value of KL6 in diagnosing ILD compared to traditional PFTs and support including serial KL6 measurements as part of CTD-ILD's diagnostic and monitoring algorithm, potentially leading to earlier interventions and improved disease management strategies. In our cohort, baseline KL-6 showed positive correlations with specific HRCT findings such as subpleural and septal thickening, along with esophageal dilation. Follow-up KL6 also correlated with subpleural and septal thickening, ground-glass opacities, bronchiectasis, and esophageal dilation. These correlations improve our comprehension of the biomarker's role in identifying subtle radiographic changes that are typical of early interstitial involvement before significant functional impairment becomes evident [17, 20].

Prognostic implications

The progressive increase in KL-6 levels over time, along with worsening pulmonary function tests and HRCT findings, supports its prognostic relevance. KL-6's ability to predict disease progression and potentially forecast exacerbations could be crucial for tailoring therapeutic strategies to individual patient needs, allowing for earlier and possibly more effective interventions. Furthermore, the study findings might help guide the development of therapeutic benchmarks. Changes in KL-6 levels could inform treatment adjustments, similar to biomarkers used in other systemic diseases. This approach could lead to more dynamic and responsive treatment strategies in CTD-ILD, optimizing patient outcomes based on biomarker trajectories [14, 15].

Integration into clinical practice

Despite the promising implications of our findings, the integration of KL-6 into routine clinical practice requires careful consideration. The variability in KL-6 response among different CTD-ILD subtypes and its interactions with other clinical parameters suggest that it should not be used in isolation. A combined approach, utilizing KL-6 alongside PFTs, HRCT, and clinical assessment, is advocated to enhance diagnostic accuracy and disease monitoring.

Limitations

The limitations of our study include a small sample size and its unicentric design, which may restrict the generalizability of the results. Additionally, while PFTs were consistently performed for all participants at follow-up, serial KL-6 measurements were obtained only in a subset, limiting our ability to fully evaluate the biomarker's prognostic value across the entire cohort.

Future research directions

Future studies should aim to refine the predictive accuracy of KL-6 by establishing more definitive thresholds that are sensitive and specific to the various phenotypes of CTD-ILD. Longitudinal studies involving larger cohorts would help validate our findings and possibly uncover additional biomarkers that can be integrated into a multimodal diagnostic and monitoring strategy. Such research could pave the way for precision medicine in ILD treatment, where biomarkers guide clinical decisions, improving both the efficacy and safety of therapies [5, 22].

Conclusion

In summary, the findings of this study underscore the critical significance of KL-6 as a biomarker for comprehending and addressing CTD-ILD. Through its ability to offer crucial information on disease activity, advancement, and reaction to interventions, KL-6 stands out as a valuable tool in fine-tuning approaches to these intricate conditions. Its integration into clinical practice has the potential to greatly elevate patient care standards and overall outcomes in managing CTD-ILD. Moreover, with more research and refinement, KL-6 shows promise as a key part of personalized medicine strategies to improve treatment effectiveness for

individuals with CTD-ILD. By using KL-6 assessments along with other diagnostic measures, healthcare providers can better customize their treatment approaches for improved long-term outcomes in patients facing these challenging conditions.

The novelty of this study lies in the longitudinal analysis of serial KL-6 measurements, revealing their strong correlations with both pulmonary function tests and HRCT findings over time. This highlights KL-6 not only as a diagnostic tool but also as a dynamic marker for monitoring disease progression and therapeutic response. The study provides compelling evidence supporting the integration of KL-6 into routine clinical practice for a more personalized and precise management of CTD-ILD. The possible clinical implications include earlier detection of disease progression, better monitoring of treatment efficacy, and potentially improved patient outcomes through more tailored therapeutic interventions.

Abbreviations

CTD	Connective Tissue Disease
CTD-ILD	Connective Tissue Disease-Associated Interstitial Lung Disease
DLCO	Diffusing Capacity for Carbon Monoxide
FEV1	Forced Expiratory Volume in One Second
FVC	Forced Vital Capacity
HRCT	High-Resolution Computed Tomography
IIM	Idiopathic Inflammatory Myopathies
ILD	Interstitial Lung Disease
KL-6	Krebs von den Lungen-6
LIP	Lymphoid Interstitial Pneumonia
MSA	Myositis Specific Antibodies
NSIP	Non-Specific Interstitial Pneumonia
OP	Organizing Pneumonia
PFTs	Pulmonary Function Tests
SD	Standard Deviation
UIP	Usual Interstitial Pneumonia

Acknowledgements
We thank the patients for their participation and the staff at Hospital Universitario La Paz for their support.

Submission declaration
All authors have reviewed and approved the manuscript prior to its submission.

Clinical trial number
Not applicable.

Patient and public involvement
Not applicable.

Additional information
Not applicable.

Authors' contributions
JAT conceptualized and designed the study, performed initial data analysis, managed patient follow-ups, led statistical analysis, interpreted the data, drafted the manuscript, and provided overall supervision. OPF collected clinical data and provided substantial manuscript revisions. MFV conducted HRCT imaging studies and contributed to radiological data interpretation. LGC performed PFTs and contributed to data collection and interpretation. JJRB provided expertise in data interpretation and contributed to the analysis of clinical implications. All authors critically reviewed the manuscript and provided final approval.

Funding
Open Access fees funded by Boehringer Ingelheim Spain. Boehringer Ingelheim was given the opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations in relation to potential mention of BI substances.

Availability of data and materials
The research data supporting the results of this manuscript are available upon request. Interested researchers can contact the corresponding author.

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Commission of the Hospital Universitario La Paz (Approval Number: PI-5929). All participants provided informed consent to participate in the study. The authors have reviewed and accepted the journal's instructions for authors and comply with all conditions therein.

Consent for publication
Not applicable as this manuscript does not contain any individual person's data in any form (including individual details, images, or videos).

Competing interests
The authors declare no competing interests.

Author details
[1]Systemic Autoimmune Diseases Unit, Internal Medicine Department, Madrid, Spain. [2]Internal Medicine Department, Complejo Hospitalario Universitario de A Coruña, A Coruña, Spain. [3]Radiology Department, Hospital Universitario La Paz, Madrid, Spain. [4]Neumology Department, Hospital Universitario La Paz, Madrid, Spain.

Received: 19 May 2024 Accepted: 3 September 2024
Published online: 05 December 2024

References

1. Oliveira DS, Araújo Filho J de A, Paiva AFL, Ikari ES, Chate RC, Nomura CH. Idiopathic interstitial pneumonias: Review of the latest American Thoracic Society/European Respiratory Society classification. Radiologia Brasileira. 2018;51(5):321–327. https://doi.org/10.1590/0100-3984.2016.0134.
2. Mlika M, Braham E, Mezni F. Interstitial lung disease: Elementary lesions and diagnosis. Semin Diagn Pathol. 2018;35(5):288–96. https://doi.org/10.1053/j.semdp.2018.08.001.
3. Ruaro B, Matucci Cerinic M, Salton F, Baratella E, Confalonieri M, Hughes M. Editorial: Pulmonary fibrosis: One manifestation, various diseases. Front Pharmacol. 2022;13:1027332. Published 2022 Oct 17. https://doi.org/10.3389/fphar.2022.1027332.
4. Cerro Chiang G, Parimon T. Understanding Interstitial Lung Diseases Associated with Connective Tissue Disease (CTD-ILD): Genetics, Cellular Pathophysiology, and Biologic Drivers. Int J Mol Sci. 2023;24(3):2405. https://doi.org/10.3390/ijms24032405.
5. Mathai SC, Danoff SK. Management of interstitial lung disease associated with connective tissue disease. BMJ. Published online February 24, 2016:h6819. https://doi.org/10.1136/bmj.h6819.
6. Geerts S, Wuyts W, Langhe ED, Lenaerts J, Yserbyt J. Connective tissue disease associated interstitial pneumonia: a challenge for both rheumatologists and pulmonologists. Sarcoidosis, Vasculitis and Diffuse Lung Diseases. 2017;34(4):326–35. https://doi.org/10.36141/svdld.v34i4.5894.
7. Antin-Ozerkis D, Hinchcliff M. Connective Tissue disease-associated interstitial lung disease. Clin Chest Med. 2019;40(3):617–36. https://doi.org/10.1016/j.ccm.2019.05.008.
8. Maher TM. Interstitial Lung Disease: A Review. JAMA. 2024;331(19):1655–65. https://doi.org/10.1001/jama.2024.3669.
9. Takei R, Matsuda T, Fukihara J, et al. Changes in patient-reported outcomes in patients with non-idiopathic pulmonary fibrosis fibrotic interstitial lung disease and progressive pulmonary fibrosis. Front Med

(Lausanne). 2023;10:1067149. Published 2023 Jun 30. https://doi.org/10.3389/fmed.2023.1067149.
10. Castelino FV, Moua T. Detection and management of interstitial lung diseases associated with connective tissue diseases. ACR Open Rheumatol. 2021;3(5):295–304. https://doi.org/10.1002/acr2.11253.
11. Zhang H, Chen L, Wu L, et al. Diagnostic and prognostic predictive values of circulating KL-6 for interstitial lung disease. Medicine. 2020;99(16):e19493. https://doi.org/10.1097/md.0000000000019493.
12. Zhang T, Shen P, Duan C, Gao L. KL-6 as an immunological biomarker predicts the severity, progression, acute exacerbation, and poor outcomes of interstitial lung disease: a systematic review and meta-analysis. Front Immunol. 2021;12. https://doi.org/10.3389/fimmu.2021.745233
13. Demirdöğen E, Dilektaşlı AG, Öztürk NAA, et al. Serum Krebs von den Lungen-6: promising biomarker to differentiate CPFE from IPF. Sarcoidosis Vasc Diffuse Lung Dis. 2022;39(4):e2022035–e2022035. https://doi.org/10.36141/svdld.v39i4.11344.
14. Lee JS, Lee EY, Ha YJ, Kang EH, Lee YJ, Song YW. Serum KL-6 levels reflect the severity of interstitial lung disease associated with connective tissue disease. Arthritis Research & Therapy. 2019;21(1). https://doi.org/10.1186/s13075-019-1835-9.
15. d'Alessandro M, Bergantini L, Cameli P, et al. Krebs von den Lungen-6 as a biomarker for disease severity assessment in interstitial lung disease: a comprehensive review. Biomark Med. 2020;14(8):665–74. https://doi.org/10.2217/bmm-2019-0545.
16. Wang Y, Chen S, Zheng S, et al. The role of lung ultrasound B-lines and serum KL-6 in the screening and follow-up of rheumatoid arthritis patients for an identification of interstitial lung disease: review of the literature, proposal for a preliminary algorithm, and clinical application to cases. Arthritis Res Ther. 2021;23(1). https://doi.org/10.1186/s13075-021-02586-9.
17. Lederer C, Mayer K, Somogyi V, et al. Krebs von den Lungen-6 as a Potential Predictive Biomarker in Fibrosing Interstitial Lung Diseases. Respiration. 2023;102(8):591–600. https://doi.org/10.1159/000531945.
18. Sieiro Santos C, Antolín SC, Lorenzo JD la C, et al. KL6 and IL-18 levels are negatively correlated with respiratory function tests and ILD extent assessed on HRCT in patients with systemic sclerosis-related interstitial lung disease (SSc-ILD). Semin Arthritis Rheum. 2024;65:152366. https://doi.org/10.1016/j.semarthrit.2024.152366.
19. Hu Y, Wang L, Jin Y, et al. Serum Krebs von den Lungen-6 level as a diagnostic biomarker for interstitial lung disease in Chinese patients. Clin Respir J. 2015;11(3):337–45. https://doi.org/10.1111/crj.12341.
20. 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):2889–92. https://doi.org/10.2169/internalmedicine.50.5866.
21. Tagami Y, Hara Y, Murohashi K, et al. Comparison of Clinical Features between the High and Low Serum KL-6 Patients with Acute Exacerbation of Interstitial Lung Diseases. Can Respir J. 2021;2021:1–9. https://doi.org/10.1155/2021/9099802.
22. Oyama T, Kohno N, Yokoyama A, et al. High serum KL-6 levels predict the deterioration of pulmonary function in patients with rheumatoid arthritis. Japanese J Rheumatol. 1999;9(4):373–80. https://doi.org/10.3109/bf03041350.

Publisher's Note