KL-6 biomarker: a favor to Interstitial Lung Disease diagnosis at Patna

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ABSTRACT

KL-6, or Krebs von den Lungen-6, is a glycoprotein that is found on the surface of type II pneumocytes in the lungs. It is also present in various other epithelial cells. KL-6 has gained attention as a biomarker, particularly in the context of lung diseases, especially interstitial lung diseases (ILD). [1, 2, 3, 4]

1. **Function:** KL-6 is involved in maintaining the structural integrity of the lungs. It is a mucin-like glycoprotein, and its exact function is not completely understood. However, it is thought to play a role in the protection and repair of the alveolar epithelium.

2. **Biomarker for Lung Diseases:** Elevated levels of KL-6 in the blood have been associated with various lung diseases, especially interstitial lung diseases such as idiopathic pulmonary fibrosis (IPF), pneumoconiosis, and others. Monitoring KL-6 levels can be useful in assessing disease activity and progression. [6]

3. **Idiopathic Pulmonary Fibrosis (IPF):** KL-6 is often used as a biomarker for IPF, a progressive and fatal lung disease characterized by the scarring of lung tissue. Elevated KL-6 levels may indicate ongoing damage to the lung epithelium, and it can be a helpful tool in diagnosing and monitoring IPF.

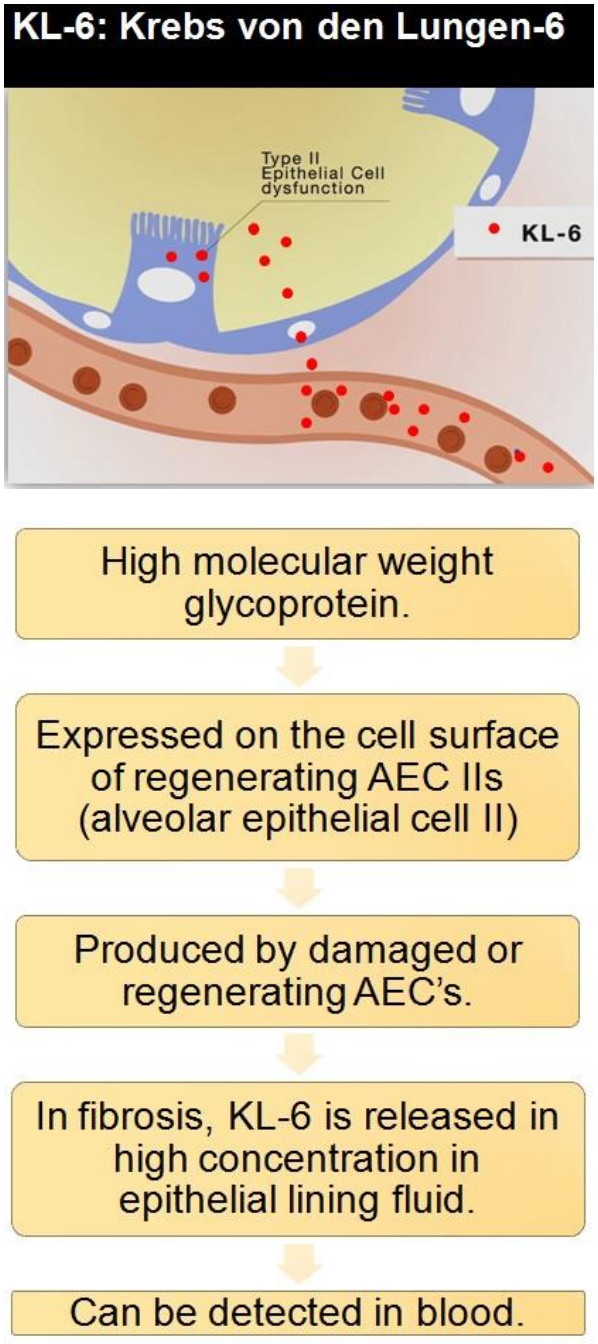
4. **Other Conditions:** Elevated KL-6 levels have also been reported in conditions beyond lung diseases, such as certain types of cancers, rheumatoid arthritis, and diabetes. However, its primary clinical use is in the context of lung diseases.

5. **Diagnostic Tool:** KL-6 is measured through blood tests. High levels of KL-6 in the blood may prompt further investigations to determine the underlying cause, especially in individuals with respiratory symptoms or suspected lung diseases.

Biomarker prevalence can be influenced by factors such as the prevalence of underlying diseases associated with KL-6 elevation, local demographics, and the availability and utilization of diagnostic tests. KL-6 is often studied and used more extensively in the context of specific lung diseases, especially interstitial lung diseases (ILD), such as idiopathic pulmonary fibrosis (IPF). [7] The prevalence of ILD, and consequently the prevalence of elevated KL-6 levels, can vary among different populations. Interstitial Lung Disease is associated with significant morbidity, mortality and increased financial burden. The overall prevalence of ILD was 20% higher in males than females. [7]

Why KL-6 is important in diagnosis?

KL-6 is considered an important biomarker, particularly in the field of respiratory medicine, and it plays a significant role in the diagnosis and management of certain lung diseases, especially interstitial lung diseases (ILD).



Idiopathic Pulmonary Fibrosis (IPF): KL-6 is commonly used as a biomarker in the diagnosis and monitoring of idiopathic pulmonary fibrosis (IPF). IPF is a progressive and often fatal lung disease characterized by the scarring of lung tissue. Elevated levels of KL-6 in the blood are associated with the ongoing damage to the alveolar epithelium, which is a feature of IPF. [8]

Interstitial Lung Diseases (ILD): Beyond IPF, KL-6 is also associated with other interstitial lung diseases. Elevated KL-6 levels can be indicative of interstitial lung involvement, and the biomarker is often measured to aid in the diagnosis and monitoring of various ILDs. [9]

Differential Diagnosis: KL-6 levels can help in differentiating between various lung diseases. While elevated KL-6 is often seen in ILDs, it may not be as elevated in other lung conditions. This specificity can be valuable in narrowing down the differential diagnosis when assessing patients with respiratory symptoms. [10]

Monitoring Disease Progression: KL-6 levels are often monitored over time to assess disease progression or response to treatment. A decrease in KL-6 levels may indicate a positive response to therapy, while persistent or increasing levels may suggest ongoing disease activity. [11]

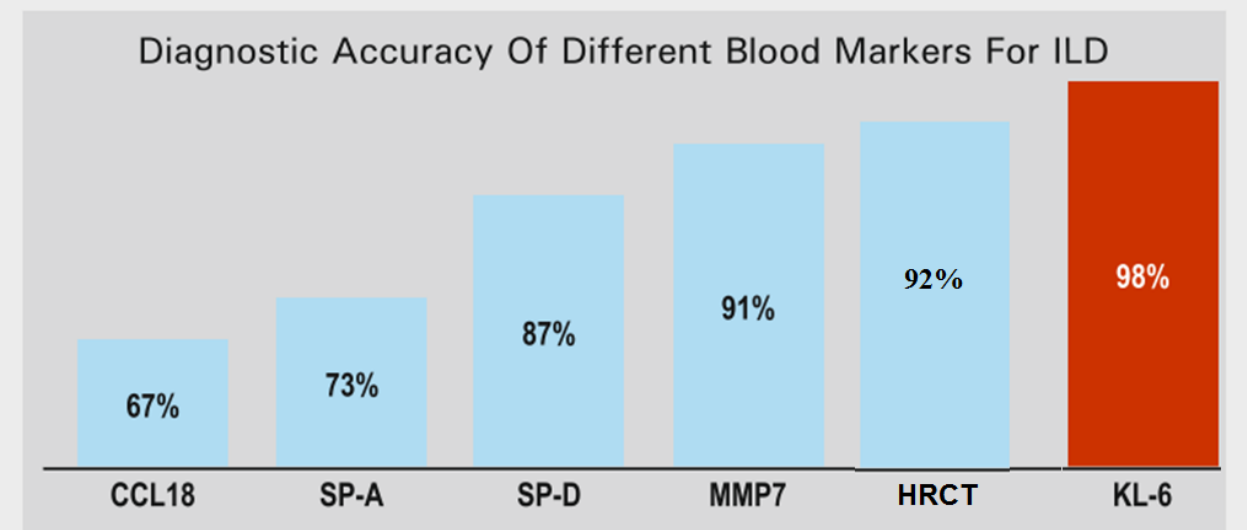
Research and Clinical Trials: KL-6 is frequently used as an endpoint or outcome measure in clinical trials and research studies related to lung diseases. It provides a quantifiable parameter for assessing treatment efficacy and disease progression.

Clinical Perspective	Analytical Perspective
1. Specific lung biomarker 2. Detecting the disease presence 3. Evaluating disease activity 4. Predicting outcomes	1. Accurate 2. Rapid 3. Reproducible 4. Non-invasive 5. Easy to perform

Diagnostic accuracy

KL-6 is a promising prognostic marker of IPF and improves survival prediction in patients with IPF. The diagnostic accuracy of KL-6 is influenced by factors such as the cutoff values used, the population being studied, and the presence of comorbidities. Elevated levels of KL-6 can be found in various lung conditions, and its interpretation often requires consideration of the patient's clinical history and additional diagnostic tests. KL-6 not only contributes to diagnosis but also has prognostic value. Higher levels of KL-6 have been associated with more severe disease and poorer outcomes in certain lung conditions. KL-6 levels can change over time, and serial measurements may provide more insights into disease progression or response to treatment. Monitoring KL-6 levels over time can enhance its diagnostic and prognostic value. [12]

It's crucial to note that while KL-6 is a valuable biomarker, it is typically used as part of a comprehensive diagnostic approach. In our diagnostic center, KL-6 gives results alongside clinical history, physical examination, imaging studies, and other laboratory tests to make a definitive diagnosis. In the laboratory set up at Patna, Bihar, we used comparison with the HRCT marker and we found KL-6 is more promising prognostics markers of ILD. In addition to its diagnostic value, KL-6 is also considered a prognostic indicator. Higher levels of KL-6 have been associated with more severe disease and poorer outcomes in certain lung conditions, providing valuable information for treatment planning and prognostic assessment. (Graph-1)

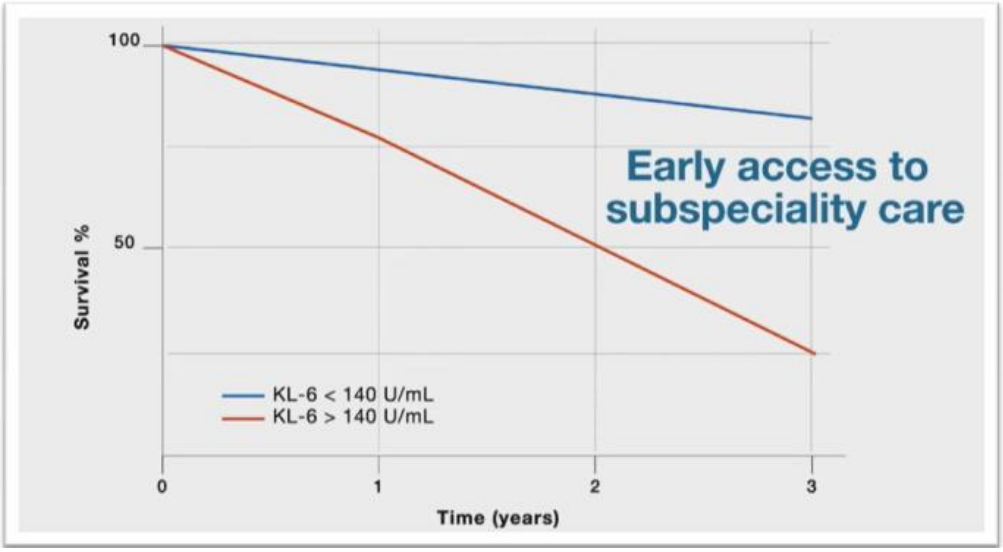


Graph-1 Studies indicated that KL-6 is having 98% accuracy compare to HRCT marker

From the graph-1, it indicate that KL-6 is promising prognostic markers of ILD and improve survival prediction in patients with ILD. This is adapted from comparative study of circulating MMP-7, CCL18, KL-6, SP-A and SP-D as disease markers of idiopathic pulmonary fibrosis. [13]

KL-6 correlation with % survival

Higher levels of serum KL-6 significantly predicted higher mortalities in patients with IPF (idiopathic pulmonary fibrosis). (Graph-2)



Graph-2, Adapted from importance of serial changes in biomarkers in idiopathic pulmonary fibrosis. [14]

KL-6 correlation with COVID

Multiple studies support KL-6 as a biomarker of COVID-19 severity and also a predictor of the prognosis of lung injury of discharged patients. [15, 16, 17] Serum KL–6 assay and NK cell analysis as part of lymphocyte phenotyping can be used to identify people with severe COVID-19. Only patients with severe pulmonary involvement had higher serum KL-6 concentrations, suggesting a predictive value and the potential utility of KL-6 testing to assess prognosis in COVID-19 patients. [18]

Conclusion

In certain research or clinical settings, the diagnostic accuracy of KL-6 can be expressed in terms of sensitivity, specificity, positive predictive value, and negative predictive value. Consequently, it's critical to consult pertinent scientific literature, recommendations, and clinical trials that are particular to the lung illness under consideration while assessing the diagnostic accuracy of KL-6. Because of its sensitivity and specificity, the author chose it as his first option for diagnosing ILDs.

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References

1. Bendstrup, Elisabeth, et al. "Challenges in the classification of fibrotic ILD." Sarcoidosis vasculitis and diffuse lung disease 32.1S (2015): 4-9.

2. Biondini, Davide, et al. "Pretreatment rate of decay in forced vital capacity predicts long-term response to pirfenidone in patients with idiopathic pulmonary fibrosis." Scientific reports 8.1 (2018): 5961.

3. Chung, Jonathan H., and Jonathan G. Goldin. "Interpretation of HRCT scans in the diagnosis of IPF: improving communication between pulmonologists and radiologists." Lung 196.5 (2018): 561-567.

4. Cottin, Vincent, et al. "Fibrosing interstitial lung diseases: knowns and unknowns." European Respiratory Review 28.151 (2019): 180100.

5. Cottin, Vincent, et al. "Presentation, diagnosis and clinical course of the spectrum of progressive-fibrosing interstitial lung diseases." European Respiratory Review 27.150 (2018): 180076.
6. Elhai, Muriel, et al. "Performance of candidate serum biomarkers for systemic sclerosis-interstitial lung disease." Arthritis & Rheumatology (2019).
7. Kaul B, Cottin V, Collard HR, Valenzuela C. Variability in global prevalence of interstitial lung disease. Frontiers in Medicine. 2021 Nov 4;8:751181.
8. Ishikawa, Nobuhisa, et al. "Utility of KL- 6/MUC1 in the clinical management of interstitial lung diseases." Respiratory investigation 50.1 (2012): 3-13.
9. Kishaba, Tomoo. "Evaluation and management of Idiopathic Pulmonary Fibrosis." Respiratory investigation (2019).
10. Kokosi, Maria A., George A. Margaritopoulos, and Athol U. Wells. "Personalised medicine in interstitial lung diseases: Number 6 in the Series “Personalised medicine in respiratory diseases” Edited by Renaud Louis and Nicolas Roche." European Respiratory Review 27.148 (2018): 170117.
11. Kreuter, Michael, et al. "Exploring clinical and epidemiological characteristics of interstitial lung diseases: rationale, aims, and design of a nationwide prospective registry-the EXCITING-ILD registry." BioMed research international 2015 (2015).
12. Kruit, A., W. B. M. Gerritsen, and N. Pot. "CA 15-3 as an alternative marker for KL-6 in fibrotic lung diseases." Sarcoidosis vasculitis and diffuse lung disease 27.2 (2010): 138-146.
13. Hamai K, Iwamoto H, Ishikawa N, Horimasu Y, Masuda T, Miyamoto S, Nakashima T, Ohshimo S, Fujitaka K, Hamada H, Hattori N, Kohno N. Comparative Study of Circulating MMP-7, CCL18, KL-6, SP-A, and SP-D as Disease Markers of Idiopathic Pulmonary Fibrosis. Dis Markers. 2016;2016:4759040. doi: 10.1155/2016/4759040. Epub 2016 May 17. PMID: 27293304; PMCID: PMC4886062.
14. Sokai A, Tanizawa K, Handa T, Kanatani K, Kubo T, Ikezoe K, Nakatsuka Y, Tokuda S, Oga T, Hirai T, Nagai S. Importance of serial changes in biomarkers in idiopathic pulmonary fibrosis. ERJ Open Research. 2017 Jul 1;3(3).
15. d'Alessandro M, Cameli P, Refini RM, Bergantini L, Alonzi V, Lanzarone N, Bennett D, Rana GD, Montagnani F, Scolletta S, Franchi F. Serum KL-6 concentrations as a novel biomarker of severe COVID-19. Journal of medical virology. 2020 Oct;92(10):2216-20.

16. d'Alessandro M, Bergantini L, Cameli P, Curatola G, Remediani L, Sestini P, Bargagli E, Siena COVID Unit. Peripheral biomarkers' panel for severe COVID-19 patients. Journal of medical virology. 2021 Mar;93(3):1230-2.
17. Bergantini L, Bargagli E, d'Alessandro M, Refini RM, Cameli P, Galasso L, Scapellato C, Montagnani F, Scolletta S, Franchi F, Valente S. Prognostic bioindicators in severe COVID-19 patients. Cytokine. 2021 May 1;141:155455.
18. Deng K, Fan Q, Yang Y, Deng X, He R, Tan Y, Lan Y, Deng X, Pan Y, Wang Y, Guan Y. Prognostic roles of KL-6 in disease severity and lung injury in COVID-19 patients: a longitudinal retrospective analysis. Journal of Medical Virology. 2021 Apr;93(4):2505-12.