SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2024; 41 (3): e2024044 DOI: 10.36141/svdld.v41i3.15689

Correlation of serum Krebs von den Lungen-6 levels with fibrosis score on high resolution chest tomography and pulmonary function parameters in treatment naïve Idiopathic Pulmonary Fibrosis

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Abstract. *Background:* While serum Krebs von den Lungen-6 (KL-6) has been found to be a helpful biomarker in interstitial lung diseases for evaluating disease severity and progression, especially in connective tissue disease-associated interstitial lung disease (CTD ILD) and idiopathic non-specific interstitial pneumonia (NSIP), data on correlation of serum KL-6 levels with radiological fibrosis and pulmonary function parameters is lacking in treatment naïve Idiopathic Pulmonary Fibrosis (IPF) patients. *Methods*: Serum KL-6 levels were measured in thirty-nine treatment naïve newly detected IPF patients using automated immunofluorescence enzyme assay (AIA) by Tosoh Corporation, bioscience division, Tokyo, Japan. Fibrosis score was calculated by independent visual assessment of the pattern and severity of abnormalities on high resolution computed tomography (HRCT) thorax. HRCT fibrosis scores were correlated with serum KL-6 levels and pulmonary function parameters like forced vital capacity (FVC), diffusion capacity of lung for carbon monoxide (DLco). *Results:* Median value of serum KL-6 levels was 1519 U/ml (range 199.41-6055 U/ml). There was positive correlation of serum KL-6 with HRCT fibrosis score ($r=0.692$, $p<0.001$) and negative correlation with FVC ($r=-0.511$, $p=0.001$) and DLco ($r=-0.354$, $p=0.043$). In the HRCT fibrosis score pattern subset analysis, the presence of reticulation revealed weak negative and statistically insignificant correlation ($r=-0.116$, $p=0.481$) while traction bronchiectasis and honeycombing exhibited statistically significant positive correlation ($r=0.425$, $p=0.007$; $r=0.584$, $p<0.001$ respectively) with serum KL-6 levels. *Conclusion*: Serum KL-6 levels showed a positive correlation with the degree of fibrotic abnormalities on HRCT thorax and pulmonary function parameters, indicating a potential use of serum KL-6 in monitoring of parenchymal fibrosis in Idiopathic Pulmonary fibrosis.

Key words: Correlation, Krebs von den lungen-6, fibrosis score, high resolution chest tomography, treatment naïve, idiopathic pulmonary fibrosis

Received: 1 February 2024
Accepted: 20 June 2024
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Introduction

To evaluate the activity and monitor the course of interstitial lung diseases (ILD), primarily the changes in patient's symptoms like dyspnea and cough, inflammation or fibrosis resolution or progression on repeated HRCT thorax, exercise testing with 1 minute sit to stand test 1(STST)/ 6 minute walk

test (6MWT) and pulmonary function testing with absolute changes in FVC/ DLco/ lung volumes are used. However, there are problems with the sensitivity, effort dependency and ease of repetition of these investigations. Furthermore, repeated computed tomography (CT) scans result in more radiation exposure. As a more convenient and reliable indicator, several blood biomarkers have been reported to be useful in predicting diagnosis or prognosis in ILD, including surfactant proteins A (SP-A) and D (SP-D), monocyte chemo-attractant proteins 1 (MCP-1) and 7 (MCP-7), chemokine ligand 18 (CCL-18), interleukin-8 (IL-8), and Krebs von den Lungen-6 (KL-6) (1-3).

KL 6/ MUC1 (Krebs von den lungen-6/ Mucin-1) (2) is expressed on the apical surface of normal glandular epithelial cells of the lung, stomach, pancreas, and breast. In the lungs, alveolar wall is composed of type I and type II alveolar cells. While type I alveolar cells lack proliferative division capacity, type II alveolar cells possess proliferative and division capacity and in the event of alveolar damage these type II alveolar cells proliferate and fill the void. Normally, KL-6 is weakly expressed in the basal cells of terminal bronchial epithelium, alveolar epithelial type II cells and serous gland cells. However, KL-6 is released in the blood stream when these cells proliferate, are stimulated or injured and the permeability of the alveolar capillary barrier is altered. Hence, serum KL-6 is considered marker of alveolar damage in ILD. KL-6 has a prognostic value, as high levels >1000 U/ml are associated with a bad prognosis (4). However, literature on correlation of serum KL-6 levels with radiological fibrosis and pulmonary function parameters is lacking in treatment naïve IPF patients.

Therefore, the aim of our study was to estimate correlation of serum KL-6 levels with HRCT fibrosis score and lung function parameters in treatment naïve IPF patients.

Materials and method

Study design and participants

This was a cross-sectional analytical study conducted at a tertiary health care institute of North India from June 2022 to September 2023 after approval from the Institutional Ethics Committee (IEC No: 22/288). Diagnosis of IPF was made based on latest official ATS/ERS/JRS/ALAT Clinical Practice Guideline (5). Based on sample size estimation using a previous study (6) and inclusion criteria, 39 treatment naïve newly detected IPF patients at our ILD clinic were recruited in the study. Exclusion criteria comprised patients having acute exacerbation of ILD, history of pneumonia within the past month, individuals with concurrent lung cancer, active pulmonary tuberculosis, and those not giving consent.

Baseline investigations and workup

All the patients included in the study had undergone detailed history taking for symptoms, CTD symptoms, exposure assessment and baseline blood investigations like pulmonary function test (inclusive of spirometry, DLco and body plethysmography {in 33 patients}), exercise testing with 6MWT, HRCT thorax (as per protocol for IPF) and serological workup for anti-nuclear antibody (ANA), angiotensin converting enzyme (ACE), rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP), erythrocyte sedimentation rate (ESR), c-reactive protein (CRP) and creatine phosphokinase - n acetyl cysteine (CPK-NAC) {due to unavailability of myositis panel} as a part of routine workup. 6 patients also underwent bronchoalveolar lavage in view of probable IPF pattern on HRCT thorax. Data of all patients was taken up under departmental multi-disciplinary discussion (MDD) to achieve diagnosis of IPF.

Serum KL-6 assessment

An intravenous fasting 5 ml blood sample was collected in plain red-topped vacutainers in an aseptic condition. Following the collection of whole blood, a clotting period of 15–30 minutes at room temperature was observed. Subsequently, centrifugation at 1,000–2,000 x g for 10 minutes was conducted, yielding the supernatant serum. After centrifugation, the serum was promptly transferred into a clean Polypropylene tube using a Pasteur pipette, with careful handling at 2–8°C. Subsequently, the serum was divided into 0.5 ml aliquots and stored at −20°C. Samples were then analyzed for estimation of serum KL-6 by automated immunofluorescence assay (AIA) with ST AIA-PACK KL-6 manufactured by Tosoh Corporation − Bioscience Division, Tokyo, Japan. It is an immunoenzymometric assay that is performed entirely in the ST AIA-PACK KL-6 test

cups. Fluorescence kinetics served as the foundation for measurement, and the test was conducted using reagents that had been lyophilized and made ready to use. A standardized test cup protocol was used for consistent performance. First, the seal of the test cup was broken by an instrument, followed by dissolution with the blood specimen and the diluent. Next, the sample was incubated, and washing was performed, followed by the addition of an anti-KL-6 monoclonal antibody. Finally, the sample was incubated with a fluorogenic substrate, 4-methylumbelliferyl phosphate (4MUP). The amount of enzyme-labeled monoclonal antibody that binds to the beads is directly proportional to the KL-6 concentration in the test sample.

HRCT fibrosis score assessment:

Quantitative CT scans help in predicting mortality in pulmonary fibrosis patients (7). Hence, we included an HRCT scan of the thorax in our assessment of IPF. HRCT findings were evaluated and scored for fibrosis score by a radiologist. Scoring was done as per the protocol followed in the study by Keishi Oda et al (8). HRCT findings were graded on a scale of 1–4 based on the classification system: 1. normal attenuation; 2. reticular abnormality; 3. traction bronchiectasis; and 4. honeycombing. The presence of each of the above four HRCT findings was assessed independently in three (upper, middle and lower) zones of each lung. The upper lung zone was defined as the area of the lung above the level of the tracheal carina, the lower lung zone was defined as the area of the lung below the level of the inferior pulmonary vein and the middle lung zone was defined as the area of the lung between the upper and lower zones. The extent of each HRCT finding was determined by visually estimating the percentage of parenchymal involvement in each calculated by multiplying the percentage of the area by the grading scale score. The six zone scores were averaged to determine the total score for each patient. The highest score was 400 and the lowest score was 100.

Statistical analysis:

Statistical analysis was done using IBM statistical software SPSS Version 26.0. The normality and skewness of data was checked using Shapiro-Wilk test. Descriptive statistics was presented as mean and standard deviation (for normally distributed data) and median and interquartile range (for skewed data). Categorical data was presented as frequencies and percentages. Pearson correlation coefficient 'r' was calculated to find the strength and direction of relationship between the independent and dependent variables following a parametric (normal) distribution. Correlations involving nonparametric (non-normal) variables were done by calculating spearman's rho coefficient. In this study serum KL-6 levels followed a non-parametric distribution. The results were presented in tables, graphs and charts. Correlations were depicted in scatterplots with R-squared values and univariate linear regression equations.

Results

During study duration we screened 220 patients at our ILD clinic, out of which 56 patients were suspected to have IPF. After exclusion of patients (Figure 1), 39 were included in the study.

Baseline demographics and characteristics

Out of 39 patients, 27 (69.2%) patients were males and 12 (30.8%) were females. The mean age of the cohort was 63.03 ± 6.94 years. The average age of males was 65.70 ± 6.47 years and 60.91 ± 3.05 years in females. Mean BMI was 22.62 ±2.88 kg/m2. While all the patients had shortness of breath and dry cough, 61.5 % patients had fatigue, 43.5 % patients had weight loss and 33.33% patients had gastroesophageal reflux disease (GERD) symptoms. There was no known family history of IPF in any patient. Out of 39 patients, 11 patients (28.21%) suffered from at least 1 comorbidity with 7 (17.95%) of them having diabetes mellitus (DM), 6 (15.38%) had systemic hypertension (HTN) and 8 (20.5 %) had pulmonary hypertension based on 2D Echocardiography. The overall baseline demographic and symptoms profiles are summarized in Table 1.

Pulmonary function test parameters

Majority of patients had very severe restriction (n=13; 33%), followed by severe restriction (n=12; 31%), moderately severe restriction (n=12; 31%) and moderate restriction (n=2; 5%). Overall, 6 (15%)

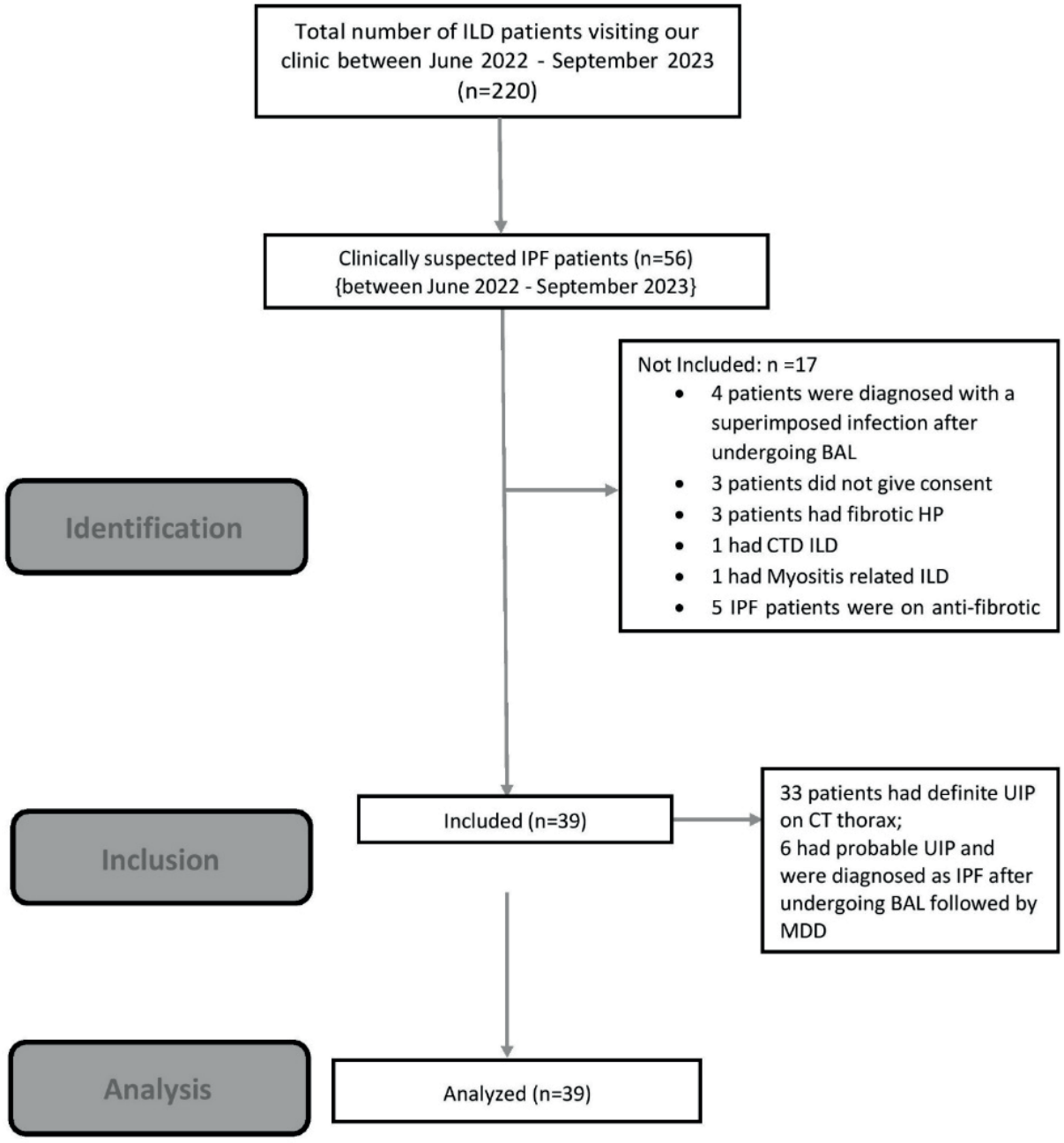

Figure 1. STROBE Flow Chart: Strengthening the Reporting of Observational Studies in Epidemiology: Abbreviations: ILD – Interstitial Lung Disease, IPF – Idiopathic Pulmonary Fibrosis, BAL – Broncho-alveolar lavage, HP – Hypersensitivity Pneumonitis, CTD – Connective Tissue Disease, UIP – Usual Interstitial Pneumonia, CT – Computed Tomography, MDD – Multi- disciplinary Discussion.

patients were unable to perform DLCO and body plethysmography despite all attempts. Among those who could perform, 24 (62 %) patients had a severely reduced DLCO (<40% predicted) and 9 (23%) patients had a moderately reduced DLCO (40-60%). Six-minute walk test was performed by all patients wherein the range of six-minute walk distances was 220 to 350 meters with a median of 300 meters. The desaturation range was from 0 to 9% with a median of 2%. Various lung function parameters of our cohort are depicted in Table 2.

Table 1. Demographic variables and symptoms in the study population (n=39).

Variables	Number	Percentage
Gender		
Male	27	69.20 %
Female	12	30.80%
Smokers	19	52.78%
Occupation		
Farmer	27	69.20 %
Homemaker	9	23.10%
Shopkeeper	1	2.60 %
Teacher	2	5.1%
Symptoms		
Shortness of Breath	39	100.00%
Cough	39	100.00%
Gastro esophageal reflux disease	13	33.33%
Fatigue	24	61.5%
Weight loss	17	43.6%
Comorbidities		
Diabetes Mellitus	15	12.8%
Hypertension	4	10.3%
Both Diabetes and Hypertension	2	5.1%
Pulmonary Hypertension	8	20.5%

Table 2. Distribution of various pulmonary function test parameters in the study population (n=39).

Variables	Mean ± SD	Median (Range)
FVC %age predicted	42.87± 11.24	42 (18-63)
FVC Z score	- 3.80 ± 0.74	-3.87 (-5.47 to -2.47)
DLCO %age predicted	31.12 ± 12.67	29 (11-54)
DLCO Z score	-4.59 ± -6	-4.73 (-6 to -3)
TLC %age predicted	39.21 ± 11	40 (20-62)
RV %age predicted	30.42 ± 7.85	31 (15-44)
6MWD (m)	289.23 ± 38.34	300 (220 -350)
Desaturation	2.58 ± 1.80	2 (0-9)

Abbreviations: SD: Standard Deviation; FVC: Forced vital capacity; DLCO: Diffusion capacity of lung for carbon monoxide; RV: Residual Volume; TLC: Total Lung Capacity; 6MWD: Six-minute Walk Distance.

CT fibrosis score

In our study, HRCT fibrosis score ranged from 146.67 to 302.5, out of which 1 (2.56 %) patient was in the 100-150 range, 18 (46.15%) were in 150-200, 14 (35.90%) between 200-250, 5 (12.8%) in 250 – 300 and 1 (2.56%) above 300 range. Table 3 depicts the HRCT fibrosis scores of the cohort.

Analysis of Serum KL-6

Serum KL-6 values were non-parametrically distributed with median value of 1519 U/ml (199.41-6055). 33 % of IPF patients had serum KL-6 value between 600-1500, 28 % patients had 1500-2500, 23% had value > 2500 and 15 % had value less than 600 (Table 3).

Table 3. Distribution of HRCT fibrosis scores and serum KL-6 value in our study population (n=39).

Parameters	**Mean ± SD**	**Median (Range)**
Normal sub score	269.62 ± 88.0	290 (80-415)
Reticulation sub score	213.59 ± 99.51	210 (60-520)
Traction Bronchiectasis sub score	301.67 ± 136.43	285(90-630)
Honeycombing sub score	482.82 ± 285.23	460 (0-1080)
Total HRCT fibrosis score	211.28 ±38.74	203.33(146.67-302.50)
Serum KL-6 (U/ml)	**Number of Patients**	**Percentage**
<600	6	15.38%
600-1500	13	33.33%
1500-2500	11	28.21%
>2500	9	23.8%

Abbreviations: Abbreviations: SD: Standard deviation; KL-6: Krebs Von den Lungen-6.

Correlations of serum KL-6 with HRCT fibrosis score

Serum KL-6 had a correlation coefficient of 0.692 with HRCT Fibrosis score (Figure 2). On univariate analysis of each component of HRCT fibrosis score with serum KL-6 levels traction bronchiectasis and honeycombing had correlation coefficient of 0.425 and 0.584 respectively and the correlation was statistically significant (p= 0.007 and < 0.001 respectively) while reticulation had a correlation coefficient of -0.116 (p=0.481) as shown in Figure 3.

Correlations of serum KL-6 with pulmonary function parameters

Serum KL-6 was found to have a correlation coefficient of -0.412 (p=0.009), -0.411 (p=0.009), -0.413 (p= 0.009) and 0.476 (p< 0.001) with FVC z score, carbon monoxide transfer coefficient (Kco) z score, total lung capacity (TLC) and 6 minute walk distance (6MWD) respectively in our cohort of IPF patients as depicted in Figure 4. We also found correlation of FVC z score with HRCT fibrosis score to be -0.388 (p=0.015) as depicted in Figure 5.

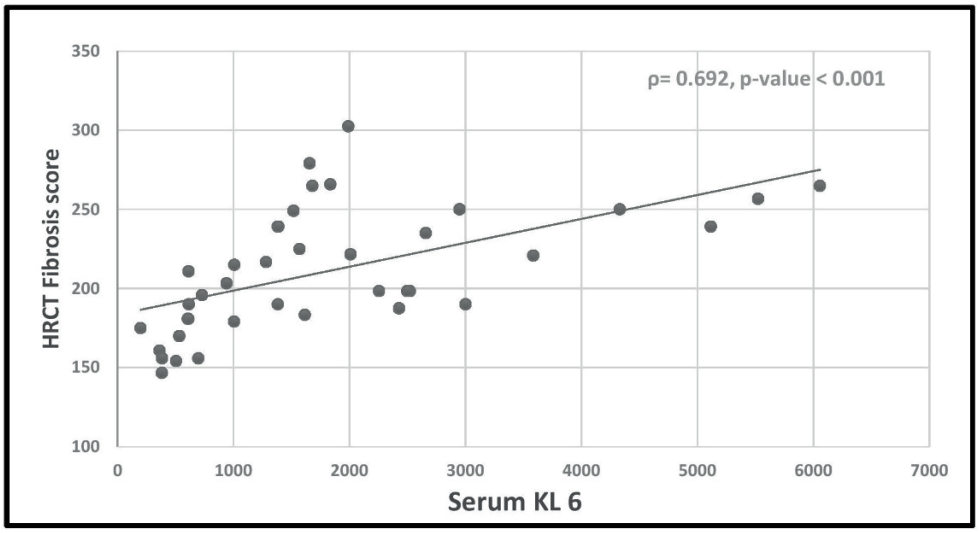

Figure 2. Correlation of serum KL-6 levels with HRCT fibrosis score (ρ: Spearman correlation, HRCT: High-resolution computed tomography, KL-6: Krebs von den Lungen-6).

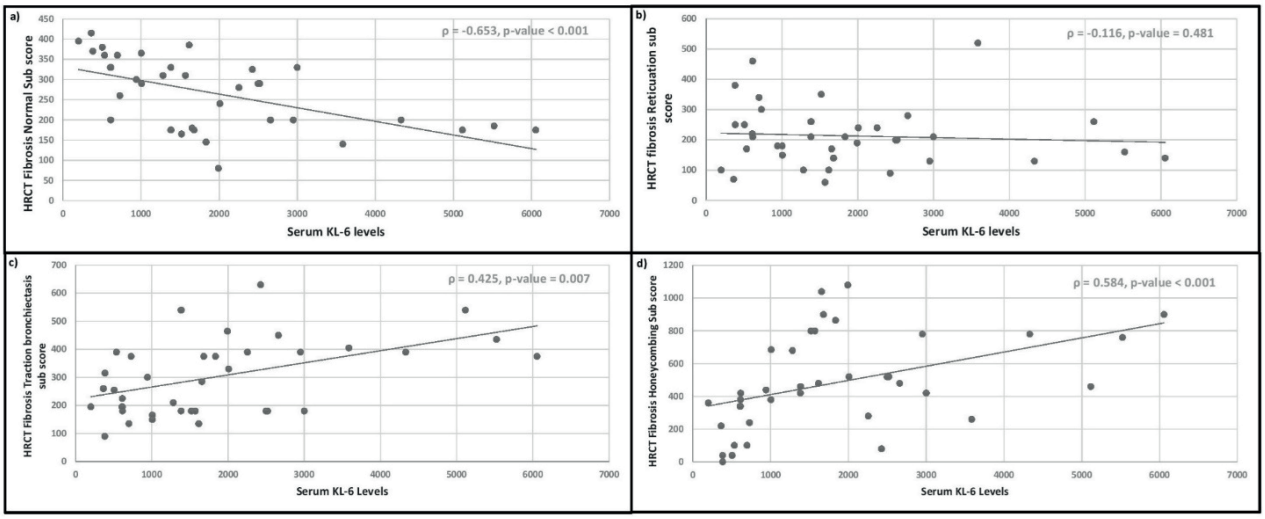

Figure 3. Correlation of Serum KL-6 Levels with HRCT fibrosis sub-scores; a) Normal sub-score, b) Reticulation sub-score, c) Traction Bronchiectasis, d) Honeycombing sub-score. (ρ: Spearman correlation, HRCT: High-resolution computed tomography, KL-6: Krebs von den Lungen-6).

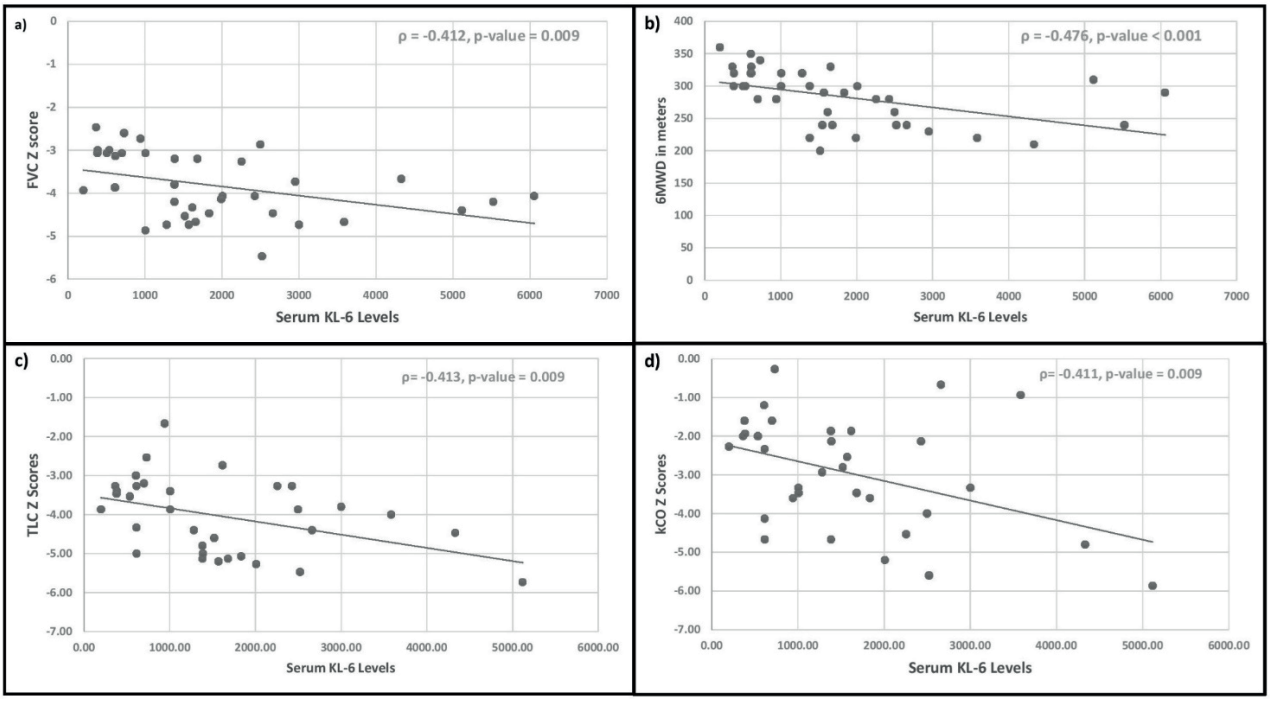

Figure 4. Correlation of Serum KL-6 Levels with a) FVC z score, b) 6MWD, c) TLC z score, d) Kco z score. (ρ: Spearman Correlation, KL-6: Krebs von den Lungen-6, FVC: Forced vital capacity, 6MWD: Six-minute walk distance in meters, TLC: Total lung capacity, Kco: Carbon monoxide transfer coefficient).

Correlation of serum KL-6 with lung function and HRCT fibrosis scores based on gender distribution

In a sub-group analysis comparing serum KL-6 levels in the male and female patients, we obtained similar correlations as in the overall group although statistical significance was not achieved in all of them likely due to the limited sample size. In male patients, serum KL-6 was found to have Spearman correlation coefficients of -0.501 ($p = 0.008$), -0.332 ($p = 0.122$), -0.778 ($p < 0.001$), and 0.711 ($p < 0.001$) with FVC

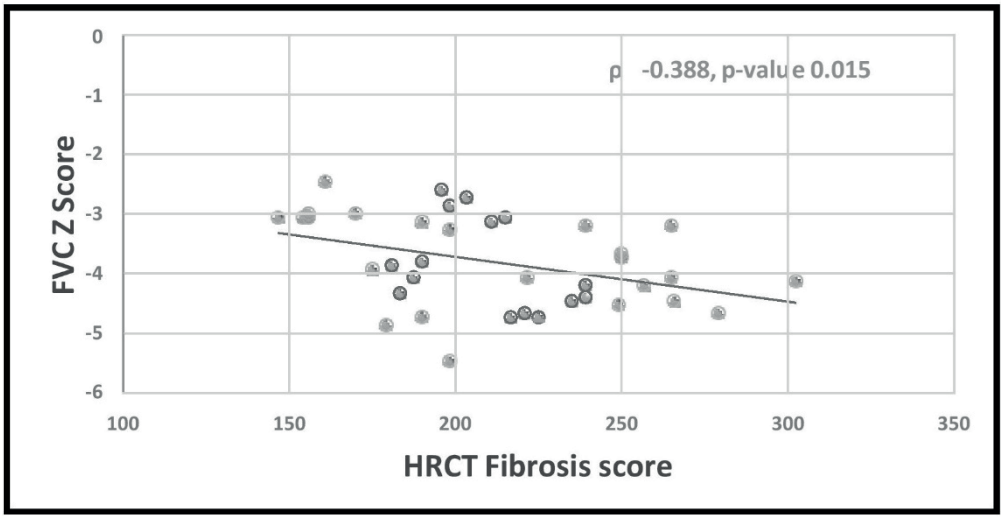

Figure 5. Correlation of Serum FVC z score with HRCT fibrosis scores (ρ: Spearman correlation, HRCT: High-resolution computed tomography, FVC: Forced vital capacity).

z score, K_{CO} z score, 6MWD, and HRCT fibrosis scores respectively. In the females, the correlation coefficients for the same parameters were -0.498 (p = 0.099), -0.608 (p = 0.062), -0.691 (p = 0.013), and 0.594 (p = 0.042) in that order.

Discussion

Our study elucidates the relationship between serum KL-6 levels with the proportion of fibrosis on HRCT thorax, and association with clinical symptoms and lung function parameters in treatment naïve IPF patients.

Median value of serum KL-6 in our study was 1519 U/ml which is comparable to results of most international studies on evaluation of serum KL-6 levels in IPF patients. A study by Majewski Sebastian et al (9) compared serum level of KL-6 in IPF patients (n=28) and controls (n=20) and reported that median serum KL- 6 values in IPF patients and controls was 1277.00 U/ml (727.8–1755) and 464.1 U/ml (221.4– 635.9) respectively. Similarly, Wakamatsu et al (10) studied prognostic value of serum KL-6 in 66 IPF patients and reported a median range of 964.5 U/ml. Another study by Millan Billi et al (11) evaluated serum KL-6 levels in normal and ILD patients and reported a value of serum KL-6 greater than 425 U/mL having excellent sensitivity and specificity to detect ILDs. Bonella et al (12) studied serum KL-6 levels in large cohort of European patients with common ILDs and found a mean value of 1877.9U/ ml in IPF patients. Several other studies have reported KL-6 levels ranging from 1039.7 ± 823.7 U/ml to 2975 (450-5750) U/ml in IPF patients (13, 14). Varied mean levels of serum KL-6 in different studies may be due to geographical heterogeneity and difference in fibrotic lung proportion in included patients. These findings highlight the necessity of correlating serum KL-6 levels in IPF patients with the extent of fibrosis on HRCT thorax.

In our study, serum KL-6 had a correlation coefficient of 0.692 with HRCT fibrosis score suggesting a moderate to good correlation between extent of fibrosis on HRCT of IPF patients and serum KL-6 levels. In a study by Zheng Muhan et al (15) in RA-ILD patients, correlation coefficient between serum KL-6 and HRCT fibrosis scores was 0.63 (p =0.002). The study showed that high KL-6 level was an important discriminating factor of ILD, and it might be a useful predictor for the severity of ILD. Similarly, Bonella F et al (12) reported a correlation coefficient of 0.68 (p < 0.001) between serum KL-6 levels and HRCT fibrosis score in systemic sclerosis ILD patients.

We found a negative correlation of serum KL-6 with pulmonary function parameters like FVC, DLco, Kco, TLC and 6MWD as depicted in results which is easily understood by the drop in values of these parameters with increasing fibrosis in IPF patients. In their study on ILD patients, H. Qin et al (6) also reported a negative correlation coefficient of -0.513 in

their cohort for DLco. Similarly, Majewski et al (9) studying various blood biomarkers in IPF patients found a moderately strong negative correlation of serum KL-6 with FVC percentage predicted at various time point (Baseline r = −0.67, p<0.001, 6 months r=−0.57, p<0.01, 12 months r=−0.60, p<0.001, 18 months r=−0.41, p<0.05 and 24 months r=−0.50, p<0.01). The baseline correlation coefficient was higher than our study but the overall average correlation over all time points was comparable to our study findings. One key finding in our study is that Kco also showed a negative correlation with serum KL-6 levels. We could not find any previous study correlating Kco directly with serum KL-6 levels in ILD patients.We observed a correlation of -0.388 between FVC and fibrosis score suggesting a reduced FVC with greater extent of fibrosis. In another study by Isaac BT et al (16) this correlation was -0.48. This difference might be due to different HRCT scoring system (Dutka/ Vasakova scoring system) used by these authors. In yet another study by Palermo et al (17) there was a weak linear correlation between HRCT fibrosis score and FVC % predicted (r=−0.014; p=0.9347). The authors attributed this to the variability of visual scoring systems in HRCT thorax and the analysis of only 6 zone of each lung as compared to a continuous quantitative assessment of the scans.

On univariate analysis of each component of HRCT fibrosis score with serum KL-6 levels we found that traction bronchiectasis and honeycombing had correlation coefficient of 0.425 and 0.584 respectively and the correlation was statistically significant (p=0.007 and <0.001 respectively) while reticulation had a correlation coefficient of -0.116 (p=0.481). C Zhu et al (18) examined 73 ILD patients, including 34 IPF patients and found a positive correlation (r=0.62, 0.41, p<0.05) between the serum KL-6 level and the lung HRCT reticular pattern and honeycombing scores. This difference might be due to early disease (mild restriction only) with more reticulations and less honeycombing in their cohort. As serum level of KL-6 is directly related to amount of regeneration of type II alveolar epithelial cells, the serum levels may be low in early IPF with reticulations and the levels may rise as the damage proceeds and manifest radiologically as traction bronchiolectasis/ bronchiectasis and honeycombing. This hypothesis needs to be evaluated in future longitudinal studies.

Top of FormThere are few limitations in our study. Firstly, this study was conducted in a single tertiary referral center in a time bound fashion leading to a small sample size limited to a specific geographical region. Hence, we could not perform a subgroup analysis based on severity of lung function impairment or extent of fibrosis and correlation with serum KL-6 levels. Second, normal values of serum KL-6 levels or levels in ILD from India are not available in the existing literature, hence a comparison could not to be done with normal subjects and sensitivity analysis was not possible. Third, as majority of our study participants were farmers, we cannot exclude the impact of occupational exposure to dust or fibers which they might have been unknowingly exposed to during work. However, we attempted our best to elucidate the exposure history in our study participants. Lastly, since our study population included only IPF patients, we cannot comment on correlation of serum KL-6 with fibrosis score in our subtypes of ILD like fibrotic HP, CTD- ILD or fibrotic NSIP.

Conclusion

In IPF patients, serum KL-6 levels show positive correlations with the extent of fibrosis on HRCT thorax and negative correlations with FVC and DLco, Kco, residual volume and total lung capacity. Moreover, among HRCT findings of ILD, the extent of traction bronchiectasis and honeycombing have a significant correlation with serum KL-6 levels. Further longitudinal studies including long-term follow-up and serial monitoring of serum KL-6 levels are needed to confirm these findings.

Acknowledgements: None

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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