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ORIGINAL RESEARCH

# Elevated Serum Level of Krebs von den Lungen-6 Predicts Death in Patients With Comorbid Idiopathic Pulmonary Fibrosis and Obstructive Sleep Apnea

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**Background:** Obstructive sleep apnea (OSA) is prevalent in patients with idiopathic pulmonary fibrosis (IPF). This study evaluated the prognostic significance of Krebs von den Lungen-6 (KL-6) levels in patients with comorbid OSA and IPF.

**Methods:** This retrospective research included 115 individuals diagnosed with IPF between January 2015 and December 2020, all of whom completed sleep tests and underwent measurement of serum KL-6 levels during hospitalization. To ascertain the risk factors associated with all-cause death, a multivariate Cox regression model was employed, adjusted for confounding variables of age, sex, and pulmonary function.

**Results:** During the 40-month follow-up, 24 (20.9%) deaths occurred, with 17 (28.8%) in the OSA group and 7 (12.5%) in the non-OSA group. Patients with OSA had higher baseline KL-6 levels than did those without OSA. Both apnea-hypopnea index (hazard ratio [HR] = 1.023, 95% confidence interval [CI] 1.000–1.047, $p = 0.049$) and serum KL-6 levels (HR = 1.001, 95% CI 0.999–1.002, $p = 0.032$) were identified as independent risk factors for death in multivariable Cox analysis. For the overall cohort of patients with IPF, those with a KL-6 levels ≥1200 U/mL had a higher risk of death in both univariate analysis (HR = 5.694, 95% CI 1.945–16.669, $p = 0.002$) and adjusted models (HR = 5.245, 95% CI 1.775–15.494, $p = 0.003$). In the subgroup analysis, the independent prognostic significance of KL-6 levels ≥1200 U/mL for death was evident only in IPF patients with concurrent OSA (HR = 4.887, 95% CI 1.082–22.067, $p = 0.039$), whereas it was not observed yet in IPF patients without OSA (HR = 4.652, 95% CI 0.616–35.131, $p = 0.136$).

**Conclusion:** KL-6 level is of prognostic value in patients with comorbid IPF and OSA. These findings underscore the need for sleep tests and KL-6 measurement for IPF patients at high risk.

**Keywords:** death, idiopathic pulmonary fibrosis, obstructive sleep apnea, serum Krebs von den Lungen-6

## Introduction

Idiopathic pulmonary fibrosis (IPF), marked by diffuse inflammation and fibrotic changes in both the alveoli and interstitium, represents a chronic and progressive pulmonary disorder with an undetermined etiology.[1,2] Despite the implementation of effective interventions, such as anti-fibrotic medications, to combat the advancement of fibrosis, the overall mortality of patients with IPF remains staggering, particularly among those with concomitant cardiopulmonary diseases, which may further diminish pulmonary ventilation and diffusion capacity, consequently increasing the likelihood of hypoxemia and respiratory failure.[3,4]

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The prevalence of sleep-disordered breathing is remarkably high in patients with IPF, ranging from approximately 60% to 80%, and obstructive sleep apnea (OSA) is the most prevalent type.[5–7] In contrast to patients with IPF alone, patients with comorbid IPF and OSA may experience exacerbated nocturnal desaturation due to breathing events in the context of IPF-induced hypoxia. Furthermore, OSA-related intermittent hypoxemia has been shown to accelerate clinical deterioration and increase mortality in patients with IPF,[8] highlighting the need for reliable biomarkers to predict adverse outcomes in patients with comorbid IPF and OSA.

Krebs von den Lungen-6 (KL-6) is a mucin-like glycoprotein that promotes fibrosis and prevents apoptosis in lung fibroblasts. It is predominantly expressed by injured type II alveolar epithelial cells and bronchiolar epithelial cells.[9] Serum KL-6 level serves as an indicator of alveolar epithelial impairment, such as increased alveolar wall permeability, and has been validated as a noninvasive biomarker in patients with IPF, enabling the assessment of clinical severity and prediction of adverse prognosis.[10,11] Intriguingly, increased serum KL-6 levels have been noted in patients with OSA and are inversely correlated with nocturnal saturation levels,[12,13] suggesting alveolar wall impairment in OSA. However, to the best of our knowledge, data on the relationship between KL-6 levels and prognosis of patients with IPF complicated by OSA are scarce. Given the high prevalence of comorbid OSA and IPF and the close relationship of KL-6 with both conditions, this study tested our hypothesis that serum KL-6 level can serve as an indicator for identifying individuals at an increased risk of poor prognosis in this cohort.

# Methods

## Study Population

All hospitalized adult patients (aged ≥18 years) diagnosed with IPF (n = 710) at the Department of Pulmonary and Critical Care Medicine of China-Japan Friendship Hospital and Beijing Anzhen Hospital of Capital Medical University between January 2015 and December 2020 were retrospectively investigated. Patients were included only if the following data were all documented retrospectively: 1) polysomnography or portable sleep test results, 2) pulmonary function test (PFT) results, and 3) bronchoalveolar lavage findings during hospitalization. Patients were excluded if any of the following conditions were met: 1) presence of malignant tumor; 2) diagnosis with end-stage chronic diseases, that is, New York Heart Association Classification IV heart failure and renal failure on dialysis; 3) treatment with continuous positive airway pressure (CPAP) prior to or after sleep test; 4) acute episodes of infection on admission; 5) coronary ischemic events during hospitalization; and 6) unavailability for follow-up. In total, 115 patients were included in the final analysis. All the study protocol was supervised by the Ethics Committee of Beijing Anzhen Hospital (No. 2020066X).

## Diagnosis and Evaluation of IPF

High-resolution computed tomography was performed for all patients with suspected IPF. The attending physician made the initial diagnosis of IPF, which was forwarded to a multidisciplinary team consisting of respiratory consultants, radiologists, and pathologists to arrive at a final diagnosis based on the Clinical Guidelines of the American Thoracic Society.[1,14] Demographic information and clinical characteristics at the time of diagnosis were retrospectively collected via chart review.

Fasting blood samples were obtained from all the patients via venipuncture. Serum KL-6 levels were routinely quantified using a chemiluminescence immunoassay (Dian Diagnostics, Hangzhou, China), employing a two-step sandwich immunoassay method. Serum KL-6 levels were reported in U/mL.

PFT was conducted using a Jaeger® MasterScreen Body Plethysmograph with SentrySuite® Software (CareFusion, Hoechberg, Germany), according to the American Thoracic Society/European Respiratory Society recommendation.[15] The percentage of the predicted values (% pred) were calculated for forced vital capacity (FVC) and the diffusing capacity of the lung for carbon monoxide (DLCO). Bronchoalveolar lavage was performed for all patients, and differential cell counts in bronchoalveolar lavage fluid (BALF) were analyzed according to the pertinent American Thoracic Society guideline.[16] Six-minute walking test (6 MWT) and baseline arterial partial pressure of oxygen ($PaO_2$) test in wakefulness were also conducted.

## Sleep Study

During the fully attended polysomnography (n = 69), conducted in a sleep lab, using the E-Series system for Sleep/EEG (Compumedics Ltd., Abbotsford, Victoria, Australia), nasal pressure transducers and oronasal thermocouples were used to monitor airflow. Electroencephalograms, electrooculograms, and submental electromyograms were recorded using the surface electrodes. The thoracoabdominal respiratory effort was assessed using breath-sensing plethysmography. Meanwhile, a level 3 (unattended) sleep test was conducted by using Alice PDx portable sleep diagnostic system (Philips Respironics, Murrysville, PA, USA) for 46 patients, with nasal pressure transducer and orinasal thermocouple, thoracic-abdominal respiratory inductance plethysmography and percutaneous pulse saturation recorded. Sleep data collected by same devices were scored by registered sleep technologists, based on the criteria given in the American Academy of Sleep Medicine Manual to ensure the consistency between two sleep centers.[17] Apneas without evidence of respiratory effort were scored as central, while those with respiratory effort were categorized as obstructive. The apnea-hypopnea index (AHI) quantifies the frequency of obstructive apneas and hypopneas per hour of sleep. The patients were diagnosed with OSA if their AHI exceeded 15 events/h. Oxygen desaturation index (ODI) was computed to indicate hourly desaturation ≥3% during sleep. Nocturnal minimum oxygen saturation during sleep ($MinSpO_2$) was derived directly from the system.

## Follow-Up

The study outcome was all-cause mortality. Participants were followed up until May 30, 2023, or until they were lost to follow-up, whichever occurred first. Vital status was determined by reviewing medical records and telephone interviews. The follow-up duration was calculated in months from the date of hospitalization to the censoring date.

## Statistical Analysis

The Shapiro–Wilk test was used to assess the normality of continuous variables. Data following a normal distribution were expressed as means ± standard deviations and analyzed using Student's *t*-test for group comparisons. Skewed data were described using the median (interquartile range [IQR]) and compared using the Mann–Whitney *U*-test. Categorical variables were presented as frequencies (percentages), and Pearson's chi-squared tests were used for group comparisons. Receiver-operating characteristic (ROC) analysis was employed to determine the optimal KL-6 cutoff value for predicting mortality, balancing sensitivity and specificity. In addition, conventional cutoff values for FVC (75% predicted) and ODI (15 events/h) were also utilized in the statistical analysis. Differences in survival between the groups were analyzed using the Kaplan-Meier method and the Log rank test. Cox proportional hazards regression models were constructed to survey independent risk factors for all-cause death, with adjustments for age, sex and FVC (a widely recognized risk factor of death).[9,11] Statistical analyses and data plotting were performed using JMP version 16 (SAS Institute, Cary, NC), with a $p$ value less than 0.05 deemed statistically significant.

# Results

## Clinical Characteristics of Study Population

The baseline characteristics of the 115 patients with IPF (59 with OSA and 56 without OSA) are shown in Table 1. Compared with patients without OSA (non-OSA group), those with OSA (OSA group) were older (age: 59.16±9.07 vs 65.00±8.78 years, $p = 0.001$) and more obese (body mass index: 25.29±3.84 vs 27.14±4.65 kg/m$^2$, $p = 0.022$), with significantly greater serum KL-6 levels (1022.50 [680, 1547] vs 1895 [890, 2505] U/mL, $p = 0.001$). No significant differences were found between the two groups in terms of sex, pack-years of smoking, 6 MWT, baseline $PaO_2$, PFT, or the proportion of patients who received anti-fibrotic agents. In the analysis of differential cell counts in BALF, the OSA group had a higher proportion of neutrophils than the non-OSA group did (15 [12, 20] vs 10 [7, 15] %, $p < 0.001$).

ROC analysis showed that KL-6 of 1112.5 U/mL was the optimal cutoff point for predicting death, demonstrating 87.5% sensitivity and 58.2% specificity, with an overall area under the curve of 74.2% achieved (Figure 1). For practical clinical use, a value of 1200 U/mL, which is close to both the ROC-determined cutoff and the median value (1158 U/

**Table 1** Clinical Characteristics of Study Patients (n = 115)

| Clinical Characteristics | Total (n = 115) | Non-OSA (n = 56) | OSA (n = 59) | *p* Value |
|---|---|---|---|---|
| Male (%) | 77 (50.99) | 34 (60.71) | 43 (72.88) | 0.234 |
| Age, years | 62.16 ± 9.35 | 59.16 ± 9.07 | 65.00 ± 8.78 | 0.001 |
| Body mass index, kg/m$^2$ | 26.24 ± 4.35 | 25.29 ± 3.84 | 27.14 ± 4.65 | 0.022 |
| Smoking, pack years | 20 (0, 40) | 15 (0, 40) | 20 (0, 40) | 0.547 |
| 6MWT, m | 450.00 (389.50, 520.00) | 465.00 (410.00, 528.00) | 441.50 (367.25, 498.75) | 0.335 |
| Serum KL-6, U/mL | 1158 (782, 2198) | 1023 (680, 1547) | 1895(890, 2505) | 0.001 |
| $PaO_2$, mmHg | 81.00 (73.50, 89.00) | 81.00 (73.50, 91.00) | 81.00 (73.25, 88.00) | 0.399 |
| AHI, events/h | 17.40 (11.30, 33.80) | 11.20 (5.83, 13.98) | 33.70 (26.20, 45.00) | <0.001 |
| Pulmonary function test | | | | |
| FVC, % pred | 70.46 ± 17.77 | 73.24 ± 18.08 | 67.73 ± 17.21 | 0.120 |
| DLCO, % pred | 59.35 ± 20.00 | 60.25 ± 20.47 | 58.49 ± 19.69 | 0.659 |
| BAL cellular profile, % | | | | |
| Macrophages | 75.0 (61.8, 80.5) | 74.50 (58.88, 83.00) | 75.00 (62.70, 78.50) | 0.525 |
| Neutrophils | 13 (9, 20) | 10 (7, 15) | 15 (12, 20) | <0.001 |
| Eosinophils | 1.5 (0.2, 5.0) | 2.50 (0.50, 6.88) | 1.00 (0.0, 4.00) | 0.093 |
| Lymphocytes | 7.0 (4.0, 14.0) | 7.25 (5.00, 14.38) | 6.80 (4.00, 14.00) | 0.268 |
| Anti-fibrotic agents (%) | 26 (22.61) | 11 (21.57) | 15 (23.44) | 0.812 |

**Notes**: Data are presented as mean ± standard deviation, median (interquartile range), or frequency (percentage).
**Abbreviations**: AHI, apnea-hypopnea index; BAL, bronchoalveolar lavage; DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity; KL-6, Krebs von den Lungen-6; OSA, obstructive sleep apnea; $PaO_2$, baseline arterial partial pressure of oxygen; 6 MWT, 6-min walking test; % pred, percentage of predicted values.

mL), was selected for subgrouping. A total of 58 patients with serum KL-6 levels ≥1200 U/mL experienced more frequent sleep breathing events (AHI: 24.15 [13.95, 37.43] vs 14.10 [8.55, 31.10] events/h, $p = 0.011$) and desaturation events (ODI: 21.10 [11.55, 36.13] vs 12.00 [6.40, 24.55] events/h, $p = 0.013$) and poorer lung function (FVC: 66.82 ±15.90% pred vs 74.03±18.92% pred, $p = 0.041$), compared with 57 patients with low serum KL-6 levels (Table 2).

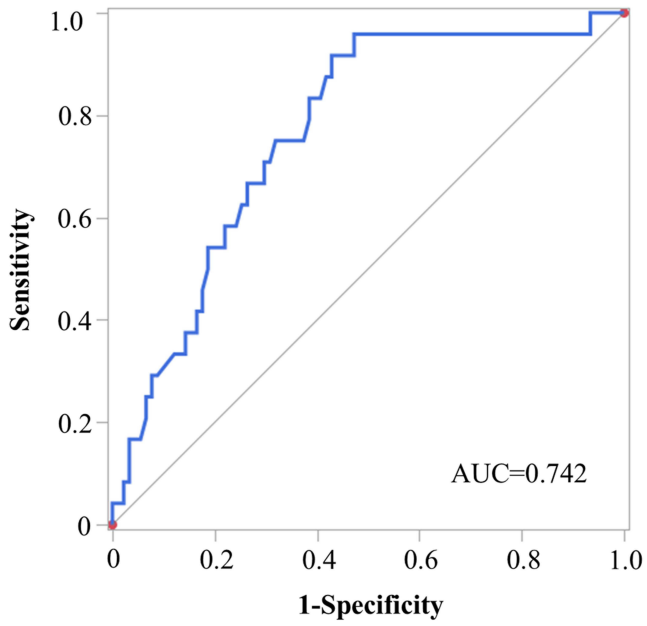


**Figure 1** Receiver operating characteristic curve of the serum KL-6 for predicting death in patients with IPF.
**Abbreviations**: IPF, idiopathic pulmonary fibrosis; KL-6, Krebs von den Lungen-6; AUC, area under the curve.

**Table 2** Comparative Analysis of the Features of Patients With IPF Categorized by Their Serum KL-6 Levels

| Variables | Serum KL-6 Level ≥1200 U/mL (n=58) | Serum KL-6 Level <1200 U/mL (n=57) | *p* Value |
|---|---|---|---|
| Sleep parameter | | | |
| AHI, events/h | 24.15 (13.95, 37.43) | 14.10 (8.55, 31.10) | 0.011 |
| $MinSpO_2$, % | 83.50 (79.00, 87.25) | 86.50 (81.50, 90.00) | 0.033 |
| ODI, events/h | 21.10 (11.55, 36.13) | 12.00 (6.40, 24.55) | 0.013 |
| BAL cellular profile, % | | | |
| Macrophages | 73.00 (61.35, 80.00) | 75.25 (58.50, 80.50) | 0.763 |
| Neutrophils | 14.50 (9.50, 20.00) | 13.00 (9.00, 18.00) | 0.367 |
| Eosinophils | 1.15 (0.15, 4.63) | 3.00 (0.50, 6.70) | 0.297 |
| Lymphocytes | 7.00 (4.25, 11.75) | 7.00 (5.50, 14.50) | 0.157 |
| Pulmonary function test | | | |
| FVC, % pred | 66.82 ± 15.90 | 74.03 ± 18.92 | 0.041 |
| DLCO, % pred | 56.49 ± 17.57 | 62.10 ± 21.90 | 0.158 |

**Notes**: Data are presented as mean ± standard deviation or median (interquartile range).
**Abbreviations**: AHI, apnea-hypopnea index; BAL, bronchoalveolar lavage; DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; KL-6, Krebs von den Lungen-6; $MinSpO_2$, minimum oxygen saturation during sleep; ODI, oxygen desaturation index; % pred, percentage of predicted values.

**Table 3** Multivariate Analysis for the Predictors of Death in Patients With IPF

| Covariates | HR | Adjusted 95% CI | *P* Value |
|---|---|---|---|
| Model 1 (with age, sex, AHI, serum KL-6 level and FVC included in multivariate analysis) | | | |
| AHI, per 1-event/h increase | 1.023 | 1.000–1.047 | 0.049 |
| Serum KL-6 level, per 1-U/mL increase | 1.001 | 0.999–1.002 | 0.032 |
| FVC, per 1% pred increase | 0.975 | 0.949–1.001 | 0.057 |
| Model 2 (with age, sex, MinSaO2, serum KL-6 level and FVC included in multivariate analysis) | | | |
| $MinSpO_2$, per 1% increase | 0.959 | 0.894–1.030 | 0.251 |
| Serum KL-6, per 1-U/mL increase | 1.001 | 1.000–1.002 | 0.009 |
| FVC, per 1% pred increase | 0.972 | 0.945–0.999 | 0.051 |
| Model 3 (with age, sex, ODI, serum KL-6 level and FVC included in multivariate analysis) | | | |
| ODI, per 1-event/h increase | 1.021 | 0.997–1.044 | 0.085 |
| Serum KL-6, per 1-U/mL increase | 1.001 | 1.000–1.002 | 0.012 |
| FVC, per 1% pred increase | 0.974 | 0.948–1.001 | 0.056 |

**Abbreviations**: AHI, apnea-hypopnea index; CI, confidence interval; FVC, forced vital capacity; HR, hazard ratio; IPF, idiopathic pulmonary fibrosis; KL-6, Krebs von den Lungen-6; $MinSpO_2$, minimum oxygen saturation during sleep; ODI, oxygen desaturation index; % pred, percentage of predicted values.

## Prognostic Factors of Death for Patients with IPF

The median follow-up duration was 40 months (IQR 22–52), and a total of 24 (20.9%) deaths (17 [28.8%] in the OSA group and 7 [12.5%] in the non-OSA group) were documented during the follow-up. AHI, ODI, FVC, and serum KL-6 levels, modeled as continuous variables, were all verified to be significant prognostic factors for death in this cohort in univariate Cox analysis (Supplementary Table 1). In multivariable models, as shown in Table 3, AHI (hazard ratio [HR] = 1.023, 95% confidence interval [CI] 1.000–1.047, $p = 0.049$) and serum KL-6 levels (HR = 1.001, 95% CI 0.999–1.002, $p = 0.032$) remained as significant risk factors for death, after adjusting for age and sex.

## Serum KL-6 Level Predicts Death in Patients with IPF

Kaplan–Meier curves were constructed to calculate the survival probability of patients. As shown in Figure 2A, OSA was significantly associated with death. Furthermore, patients with KL-6 levels ≥1200 U/mL demonstrated a higher

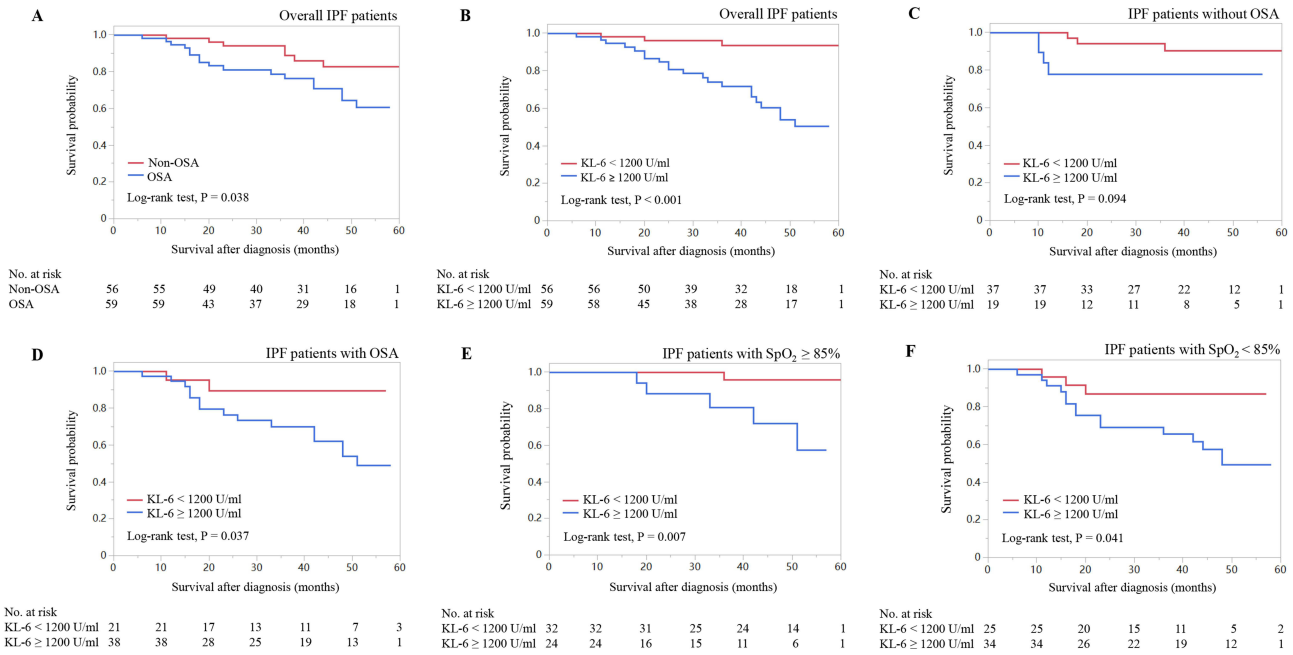


**Figure 2** Kaplan–Meier curves of survival probability of patients with IPF. Non-OSA vs OSA groups in the overall cohort of patients with IPF (**A**); KL-6 <1200 U/mL vs KL-6 ≥1200 U/mL subgroups in the overall cohort of patients with IPF(**B**); IPF patients without OSA (**C**), with OSA (**D**), with MinSpO$_2$ ≥85% (**E**), and with MinSpO$_2$ < 85% (**F**), respectively.

**Abbreviations**: IPF, idiopathic pulmonary fibrosis; KL-6, Krebs von den Lungen-6; OSA, obstructive sleep apnea.

probability of death during the follow-up (Figure 2B). However, in subgroup analysis, the significant association of serum KL-6 level ≥1200 U/mL with death was only observed in the OSA group ($\chi^2 = 4.365$, $p = 0.037$) (Figure 2C) but not in non-OSA group ($\chi^2 = 2.831$, $p = 0.092$) (Figure 2D). In the subgroups of patients with MinSpO$_2$ <85% ($\chi^2 = 4.196$, $p = 0.041$) (Figure 2E) and those with MinSpO$_2$ ≥85% ($\chi^2 = 7.193$, $p = 0.007$) (Figure 2F), KL-6 levels ≥1200 U/mL were found to be significantly associated with death.

In univariate Cox regression analysis, KL-6 level ≥1200 U/mL was found to be a significant risk factor for death in the overall IPF patient cohort (HR = 5.694, 95% CI 1.945–16.669, $p = 0.002$). In the multivariable Cox model adjusting for age, sex, and FVC, KL-6 level ≥1200 U/mL remained an independently significant predictor of death (HR = 5.245, 95% CI 1.775–15.494, $p = 0.003$) (Table 4). Notably, the independent prognostic value of KL-6 levels ≥1200 U/mL for death was only observed in the OSA group (HR = 4.887, 95% CI 1.082–22.067, $p = 0.039$) but not in the non-OSA group (HR = 4.652, 95% CI 0.616–35.131, $p = 0.136$). Furthermore, in the patient subgroups with MinSpO$_2$ <85% (HR = 3.349, 95% CI 0.965–11.629, $p = 0.057$) and MinSpO$_2$ ≥85% (HR = 11.032, 95% CI 0.929–130.987, $p = 0.057$), the prognostic value of KL-6 levels ≥1200 U/mL for death did not achieve statistical significance.

## Discussion

The primary accomplishment of this study is that it confirmed the prognostic value of KL-6 in patients with IPF and OSA. To the best of our knowledge, this is the first study to reveal the close association of KL-6 with mortality in this cohort. Practically, the easily accessible biomarker KL-6 is recommended for regular testing in patients with IPF after an OSA diagnosis to identify those at the highest risk who may require aggressive interventions in personalized treatment.

In line with previous literature,[5–7] high prevalence of OSA (51.3%) was observed in our cohort of patients with IPF. One potential hypothesis explaining the high incidence of OSA in IPF is that the reduced lung volumes observed in IPF may decrease radial traction on the upper airway, thereby increasing pharyngeal collapsibility.[18–20] Moreover, in recent decades, there has been ample evidence demonstrating the increased mortality caused by OSA associated hypoxeamia in patients with IPF.[21,22] The mechanisms contributing to the accentuated impairment of IPF by OSA remain undetermined, and we offer the following speculations. First, OSA may exacerbate systemic and local oxidative stress and inflammation,[23,24]

**Table 4** Multivariate Analysis for the Predictors of Death in the Overall IPF Patient Cohort and Subgroups

| Covariates | Overall | | Non-OSA | | OSA | | $MinSpO_2 \geq 85\%$ | | $MinSpO_2 < 85\%$ | |
|---|---|---|---|---|---|---|---|---|---|---|
| | HR (95% CI) | *p* Value | HR (95% CI) | *p* Value | HR (95% CI) | *p* Value | HR (95% CI) | *p* Value | HR (95% CI) | *p* Value |
| Age, per 1-year increase | 1.027 (0.988–1.067) | 0.181 | 1.096 (0.974–1.234) | 0.128 | 1.009 (0.963–1.056) | 0.714 | 1.202 (1.023–1.412) | 0.026 | 1.013 (0.971–1.056) | 0.553 |
| Male, yes vs no | 1.627 (0.706–3.748) | 0.253 | 2.996 (0.428–20.956) | 0.269 | 1.574 (0.585–4.234) | 0.369 | 0.775 (0.098–6.150) | 0.809 | 1.435 (0.555–3.710) | 0.456 |
| Serum KL-6≥1200 U/mL, yes vs no | 5.245 (1.775–15.494) | 0.003 | 4.652 (0.616–35.131) | 0.136 | 4.887 (1.082–22.067) | 0.039 | 11.032 (0.929–130.987) | 0.057 | 3.349 (0.965–11.629) | 0.057 |
| FVC < 75% pred, yes vs no | 1.890 (0.809–4.415) | 0.142 | 1.050 (0.190–5.800) | 0.955 | 4.620 (1.417–15.061) | 0.011 | 0.305 (0.025–3.668) | 0.349 | 2.179 (0.818–5.810) | 0.119 |

**Abbreviations**: CI, confidence interval; FVC, forced vital capacity; HR, hazard ratio; IPF, idiopathic pulmonary fibrosis; KL-6, Krebs von den Lungen-6; $MinSpO_2$, minimum oxygen saturation during sleep; OSA, obstructive sleep apnea; % pred, percentage of predicted values.

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a phenomenon also supported by the observed elevation of the neutrophil proportion in the BALF of patients with OSA in our study. Second, our study indicates an increase in alveolar wall permeability caused by OSA, as evidenced by high KL-6 levels, which aligns with findings from prior studies.[12,13] Third, the high respiratory drive and exaggerated negative thoracic pressure associated with OSA may increase the extent of capillary extravasation[25] and gastric acid aspiration,[26,27] both of which could exacerbate IPF progression. Notably, KL-6 levels can rise during IPF exacerbations and may be influenced by anti-fibrotic and anti-inflammatory therapies.[10,28] Whether treating OSA with CPAP can mitigate lung injury in ILD patients is an intriguing question that requires further evidence. Fortunately, effective CPAP therapy appears to significantly improve nocturnal sleep quality and daily activity in patients with comorbid OSA and IPF, with moderately reduced mortality reported.[29] More research is needed to unmask the underlying mechanisms through which OSA exacerbates IPF and to suggest appropriate strategies to reduce the combined damage and risk of mortality.

In an inflammatory cascade, disulfide bonds near the membrane surfaces of type II alveolar epithelial cells can break, resulting in the diffusion of KL-6 into the pulmonary epithelial lining fluid and bloodstream. As a result, elevated KL-6 levels indicate a potential for developing progressive fibrosis and, consequently, adverse outcomes in interstitial lung disease.[30–32] Indeed, the patients with IPF in our study with high KL-6 levels demonstrated significantly decreased FVC and a trend of reduced DLCO. The association between high KL-6 levels and poor survival in our study is consistent with the findings of previous studies in cohorts of patients with IPF. For instance, in Choi's study involving 96 patients with acute-exacerbated interstitial lung disease, dynamic elevation of KL-6 during hospitalization was significantly associated with higher in-hospital mortality.[9] Similarly, in Wakamatsu's study of 66 patients with stable IPF, the KL-6 levels were measured yearly, revealing that patients with either a high baseline KL-6 level (≥1000 U/mL) or an annual elevation of KL-6 exceeding 51.8 U/mL/year experienced a rapid FVC loss and poor survival.[33] It is highly likely that consecutive monitoring of KL-6 levels provides comprehensive information for risk assessment. This is especially important considering the observed stabilization or even reduction in KL-6 levels in patients with IPF receiving anti-fibrotic treatment,[34,35] which leads to a better long-term prognosis.

Circulating levels of KL-6 in the blood were positively correlated with the frequency of sleep-breathing events and severity of nocturnal desaturation, indicating that subclinical lung injury, such as increased permeability of the alveolar wall, occurs in OSA.[12,13] Based on the aforementioned understanding of KL-6 in IPF and OSA, we aimed to explore the predictive role of KL-6 in patients with both IPF and OSA. In addition to confirming a higher KL-6 level in patients with comorbid OSA and IPF than in those with IPF alone, our data validated the predictive significance of KL-6 in patients with both conditions. Interestingly, although KL-6 serves as a predictor of death in patients with IPF, its prognostic importance appears to diminish in IPF patients without OSA. It is challenging to assert that KL-6 exclusively holds prognostic significance for IPF patients with OSA and has no prognostic value for those without OSA because the smaller sample size of IPF patients without OSA and their significantly lower death rates during follow-up make it challenging to establish statistical significance. Further studies with larger sample sizes in each subgroup could offer more insights into the predictive value of KL-6 in patients with varying profiles.

## Limitations

Despite these novel findings, this study has some limitations, including its retrospective design and small sample size, which restricted the ability to incorporate sufficient variables in the multivariate analysis. We also need to acknowledge the difference between subgroups in terms of age, BMI and lung functions at baseline whose impact cannot be fully adjusted for in statistical analysis. Meanwhile, patients diagnosed with type III sleep studies were included to enlarge the sample size, which may undermine the accuracy of OSA diagnosis and grouping. Furthermore, because a relatively low proportion of patients with IPF (22.61%) have received anti-fibrotic agents and CPAP users (n = 5) were excluded, the findings of our study cannot be extrapolated to those receiving treatment with anti-fibrotic therapy or CPAP. KL-6 has been recognized as a sensitive marker for identifying the responses to effective therapy in patients with IPF.[28] Prospective studies with larger sample size (potentially involving 350 patients) are needed to validate the prognostic significance of KL-6 in patients with IPF and OSA, particularly following effective anti-fibrotic and CPAP treatment.

## Conclusions

Our study indicated that high KL-6 levels predict a poor prognosis for patients with IPF, particularly in those with comorbid OSA. Additional impact to alveolar structure might be caused by OSA at the background of fibrosis. Given the high prevalence of OSA in patients with IPF, further research is necessary to validate the prognostic significance of KL-6 in patients with IPF and OSA following effective anti-fibrotic and CPAP treatment.

## Data Sharing Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

## Statement of Ethics Approval and Informed Consent

This study was approved by the Research Ethics Board of Beijing Anzhen Hospital (No. 2020066X). Retrospective verbal consent was obtained from patients, as approved by the Ethics Board, with consent dates and relevant details documented via phone communication and recorded in the study files. Our study adheres to the principles of the Declaration of Helsinki. The identity information of all enrolled participants has been anonymized to protect their privacy.

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## Author Contributions

Fei Li: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Writing-original draft, Writing-review and editing. Jing Geng: Data curation, Investigation, Resources, Writing-review and editing. Hehe Zhang: Data curation, Formal analysis, Investigation, Resources, Writing-review and editing. Bingbing Xie: Data curation, Investigation, Resources, Writing-review and editing. Hui Zhang: Data curation, Investigation, Resources, Writing-review and editing. Jing Xie and Huaping Dai: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Writing - Original Draft, Writing-review and editing. All authors have reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage. They have agreed on the journal to which the article will be submitted and agree to take responsibility and be accountable for the contents of the article.

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## Disclosure

The authors declare no conflicts of interest in this work.

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