ORIGINAL ARTICLE

Combined use of serum KL-6 and respiratory functional parameters for identifying fibrotic lung damage in SARS-CoV-2-induced interstitial pneumonia

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ABSTRACT

Background: Post-COVID19 pulmonary fibrosis (PCPF) has been reported in a significant proportion of patients who survive the acute SARS-CoV-2 infection. Krebs von den Lungen-6 (KL-6) emerges as a marker of disease severity and progression in COVID-19-related lung involvement.

Methods: A total of 231 patients (median age (interquartile range, *IQR*), 65*[57-74]* years; 143 males) were enrolled in the study. Thirty-four had IPF, 56 sarcoidosis, 141 had been hospitalized for COVID-19. After hospital discharge (median (*IQR*), 7(*5–17*) months), a diagnosis of PCPF was made in 65/141 patients and 76/141 did not show fibrotic abnormalities. Serum KL-6 concentrations were measured by KL-6 reagent assay (AIA-CL300, Tosoh Biosciences).

Results: Most PC-nonPF patients (n=70, 92%) did not require invasive mechanical ventilation (IMV) during hospital stay, while 27 (41.5%) of PCPF patients did. KL-6 concentrations were strongly suggestive of lung fibrosis with a cutoff value of 467.8 U/mL (sensitivity 73% and specificity 66%). Model obtained though machine learning approach combined lung parameters and KL-6 values for clustering fibrotic and non-fibrotic patients with an acceptable accuracy. KL-6>765 U/mL and FVC%≤88 cluster for 67% of IPF patients, while KL-6 values ≤765U/mL and FVC >60% for 81% of PCPF patients.

Conclusion: KL-6 levels are not significantly elevated in patients undergoing IMV, indicating that IMV per se does not alter the values of this biomarker, thereby further supporting its reliability in detecting PCPF. Our study proposed a combination of KL-6 values and clinical data may lead to a further improvement in diagnostic accuracy for pulmonary fibrosis, idiopathic and secondary to COVID19.

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Key words: KL-6, pulmonary fibrosis post-COVID19, interstitial lung diseases

Background

Post-COVID-19 syndrome (also known as Long-COVID) presents with a wide spectrum of long-term clinical outcomes. It is a syndrome that mainly occurs in individuals with a history of probable or confirmed severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection encompassing a protracted course of various physical and neuropsychiatric symptoms that persist for more than 12 weeks of the onset of acute COVID-19 (1,2). Persistent symptoms following COVID-19 infection are observed in over 50% of patients during follow-up and particularly in those requiring intensive care unit admission due to the severity of disease (3). Among older individuals, post-COVID19 pulmonary fibrosis (PCPF) has been reported in a significant proportion of patients who survive the acute infection (4). In particular, the development of fibrotic remodelling may be influenced by the extent and duration of the host inflammatory response, the efficiency of viral clearance and the capacity for parenchymal cell repair in damaged lung tissue (5). Despite increasing research efforts, limited data is available on long-term pulmonary outcomes and the progression of lung injury in patients affected by post-COVID-19 syndrome (6). In this context, identifying reliable diagnostic and prognostic biomarkers is critical for monitoring and potentially predicting fibrotic progression in PCPF. Among these biomarkers, Krebs von den Lungen-6 (KL-6) emerges as a promising marker of disease severity and progression in COVID-19-related lung involvement (7–9). KL-6 is a high molecular weight mucin-like glycoprotein mainly produced by damaged or regenerating alveolar type II pneumocytes (10,11). It is recognized as a diagnostic and prognostic bioindicator of ILD (12,13), especially idiopathic pulmonary fibrosis (IPF) and progressive pulmonary fibrosis (14). KL-6 has been demonstrated a reliable biomarker of fibrotic lung involvement even in sarcoidosis patients as higher KL-6 values are reported in the fibrotic stage of sarcoidosis (Scadding stage IV) (15). Nowadays no specific biomarkers have been validated to discriminate between post-COVID19 patients developing or not PCPF. To explore this aspect, we evaluated KL-6 concentrations in serum of PCPF patients compared with IPF, PC-nonPF, sarcoidosis and healthy controls (HC). Serum KL-6 levels were integrated with clinical and functional parameters to enhance diagnostic accuracy for fibrotic ILD.

Patients and methods

Study population

A total of 231 patients (median age (interquartile range, IQR), 65 [57-74] years; 143 males and 88 females) were enrolled in the study. Multidisciplinary discussion confirmed a diagnosis of IPF according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines in 34 patients (median age (IQR), 74 (70, 77) years) (16). Fifty-six patients (median age (IQR), 58 (52, 66) years) were diagnosed with sarcoidosis according to international criteria (17) based on clinical signs, chest radiography findings and non-caseating granulomas in lymph nodes and/or endobronchial biopsy specimens. In patients with sarcoidosis, the presence of pulmonary fibrosis was defined according to high-resolution computed tomography (HRCT) findings consistent with fibrotic interstitial lung disease, in accordance with the 2022 ATS/ERS/JRS/ALAT criteria for progressive pulmonary fibrosis (PPF) (16). One-hundred forty-one patients had been hospitalized for COVID-19 between April 2020 to January 2022 in the COVID Unit at Siena University Hospital and agreed to participate in the post-COVID-19 follow-up program organized by Siena Hospital. Post-COVID19 patients with a prior diagnosis of interstitial lung disease (ILD), chronic obstructive lung disease (COPD), lung or pleural malignancies or concomitant infections were excluded from the study. After hospital discharge

(median (IQR), 7 (5–17) months), all participants underwent follow-up evaluations including physical examination, serum sampling for KL-6 assessment, lung function test (LFT) parameters, diffusing capacity of the lung for carbon monoxide (DLCO) and HRCT of the chest. The median interval between the hospital admission due to COVID-19 and the HRCT scan was 7 months (IQR 5–17 months). Thus, all HRCT assessments were performed beyond 12 weeks after the onset of COVID-19, in accordance with the accepted definition of post-COVID pulmonary fibrosis (PCPF). A diagnosis of PCPF was made in 65 out of 141 patients (median age (IQR), 73 (64, 78) years), according to HRCT features consistent with pulmonary fibrosis. Specifically, ILD was diagnosed in presence of parenchymal abnormalities suggestive of interstitial involvement, including ground-glass opacities, reticulations, inter- and intralobular septal thickening, traction bronchiectasis, architectural distortion, or volume loss, with or without associated honeycombing. These features were classified as predominantly fibrotic, inflammatory, or mixed patterns, according to the extent and nature of the findings. All HRCT examinations were interpreted by an experienced thoracic radiologist specializing in interstitial lung diseases, ensuring consistency and adherence to standardized diagnostic criteria. Seventy-six out of 141 post-COVID19 patients (median age (IQR), 62 (55, 72) years) did not show fibrotic abnormalities (PC-nonPF) at the HRCT of the chest. Twenty healthy controls (HC) (median age (IQR) 54 years (30, 62)) were also enrolled. Blood samplings for KL-6 measurement were collected from IPF and sarcoidosis patients in a stable phase of disease. All patients gave their written informed consent to participation in the study. The study was approved by the regional ethical review board of Siena, Italy (C.E.A.V.S.E. approval number Markerlung17431; approval date 15/06/2020), and complied with the declaration of Helsinki.

KL-6 assay

Serum KL-6 (sKL-6) concentrations were measured by KL-6 reagent assay (AIA-CL300, Tosoh Corporation, Tokyo, Japan) based on a chemiluminescence enzyme immunoassay (CLEIA) system. The assay is based on the agglutination of sialylated carbohydrate antigens in the serum with a KL-6-specific monoclonal antibody through an antigen–antibody reaction. The change in luminescence resulting from this interaction was measured to determine KL-6 concentrations, which were expressed in units per milliliter (U/mL). The tests were conducted according to the manufacturer's protocol.

Lung function test (LFT) parameters

Lung function tests were performed according to ATS/ERS standards (18) using a Jaeger body plethysmograph with corrections for temperature and barometric pressure. Forced expiratory volume in the first second (FEV1), forced vital capacity (FVC) and DLCO were conducted on all patients. The results are expressed as percentages.

Statistical analysis

Descriptive analysis was performed to evaluate medians and interquartile ranges or means ± standard deviations, as appropriate. Comparative analysis between fibrotic and non-fibrotic groups were performed through non-parametric test (Mann-Whitney U test). Receiver Operating Characteristics (ROC) curve was employed to analyse the diagnostic performance of KL-6 for identifying pulmonary fibrotic patients and to select the best cutoff threshold with high sensitivity and specificity. Patients were stratified according to diagnosis: IPF, sarcoidosis, PCPF and PC-nonPF. A non-parametric one-way ANOVA (Kruskal–Wallis test) and the Dunn test were performed for multiple comparisons to evaluate whether there was any significant difference in KL-6 concentrations and clinical/functional data between the disease groups and HC group. In order to discriminate fibrotic (IPF, PCPF) and non-fibrotic patients (sarcoidosis, PC-nonPF, HC) according to KL-6 concentrations and LFT parameters, we constructed a regression decision tree based on the Gini criterion. Binary classifier accuracy was assessed to create a series of test/training partitions by utilizing a confusion matrix. The best thresholds for each binary classifier based on specificity and sensitivity were determined through Youden's J method. The Spearman test was used to detect correlations between immunological and clinical findings. A p-value less than 0.05 was

considered statistically significant. Statistical analysis was performed using XLSTAT 2025, GraphPad 10.1.2 and Jamovi 2.3.21 and softwares.

Results

Study population

Table 1 reported demographic, clinical and functional parameters in patients stratified according to diagnosis and compared with HC group.

IPF and PCPF showed a predominance of male sex, as well as an older age in comparison with other subgroups (p<0.01 for both). Concerning LFTs, lowest percentages of DLco and FVC were reported in IPF patients (p<0.01). The majority of PC-nonPF patients (n=70, 92%) did not require invasive mechanical ventilation (IMV) during hospital stay, while 27 (41.5%) of PCPF patients did. Concerning radiological features, PCPF group showed fibrotic inter- or intra-lobular thickening (n=65), air trapping (n=47) and ground glass opacities (n=50), while PCnonPF showed air trapping (n=51) and ground glass opacities (n = 46). All patients with IPF showed a typical UIP pattern; 6 patients with sarcoidosis (10.7%) displayed fibrotic alterations at chest HRCT scan. Stratifying patients according to fibrotic alterations at HRCT scan, older males were reported in fibrotic group than non-fibrotic (p<0.01), as well as lowest percentages of FVC (p=0.04) and DLco (p<0.01). Demographic, clinical and functional parameters of fibrotic and non-fibrotic patients were reported in Table S1.

KL-6 analysis

Overall, the presence of pulmonary fibrosis was associated with higher KL-6 concentrations (p<0.01) (Figure 1a). ROC curve analysis to distinguish fibrosis from non-fibrosis patients showed an area under the curve of 76.5% (Figure 1b) and the best cut-off value was 467.8 U/ml with 66% specificity and 73% sensitivity.

Comparing KL-6 concentrations in disease groups and HC, the highest values were reported in IPF patients (p<0.01) (Figure 2). PCPF patients showed higher KL-6 concentrations than PC-nonPF (p=0.03) and HC (p<0.01) (Figure 2). Analogous KL-6 values were observed in HC and PC-nonPF (p=0.06).

Spearman analysis showed direct correlation between FEV1% and KL-6 in IPF patients (r=0.786, p=0.028). A decision tree model (cross-validated by confusion matrix) was used to identify the best clustering variables for fibrotic patients. The model obtained (Figure 3) using functional parameters and KL-6

Table 1. Clinical, functional and immunological features of disease groups IPF, PCPF, PC-nonPF, sarcoidosis and healthy controls (HC).

Parameters	sarcoidosis (n=56)	IPF (n=34)	PC-nonPF (n=76)	PCPF (n=65)	HC (n=20)	p values
Age, median (Q1, Q3) years	58 (52, 66)	74 (70, 77)	62 (55, 72)	73 (64, 78)	54 (30, 62)	**<0.01**
Gender, n (%)						**<0.01**
Male	32 (57%)	28 (82%)	41 (54%)	42 (65%)	11 (55%)	
Female	24 (43%)	6 (18%)	35 (46%)	23 (34%)	9 (45%)	
BMI, median (Q1, Q3)	25.0 (22.0, 28.0)	24.0 (23.5, 29.0)	29.0 (25.8, 33.2)	27.0 (24.9, 30.5)	22 (19-23)	**0.01**
KL-6 U/mL, median (Q1, Q3)	487 (399, 612)	1.345 (1.039, 2.326)	370 (273, 542)	531 (337, 737)	240 (153, 330)	**<0.01**
Lung function test parameters, median (Q1, Q3)						
DLCO%	81 (72, 98)	42 (27, 54)	76 (62, 82)	73 (64, 84)	89 (88, 91)	**<0.01**
FVC%	101 (90, 113)	72 (62, 88)	97 (89, 107)	89 (83, 104)	99 (90, 108)	**<0.01**
FEV1%	103 (87, 108)	91 (85, 98)	103 (90, 110)	93 (83, 106)	104 (99, 107)	0.08

Abbreviations: IPF, idiopathic pulmonary fibrosis; PCPF, post-COVID19 pulmonary fibrosis; PC-nonPF, post-COVID19 without pulmonary fibrosis; KL-6, Krebs von den Lungen-6; FVC, forced vital capacity; DLco, diffusing capacity of the lungs for carbon monoxide.; FEV1, forced expiratory volume in the first second.

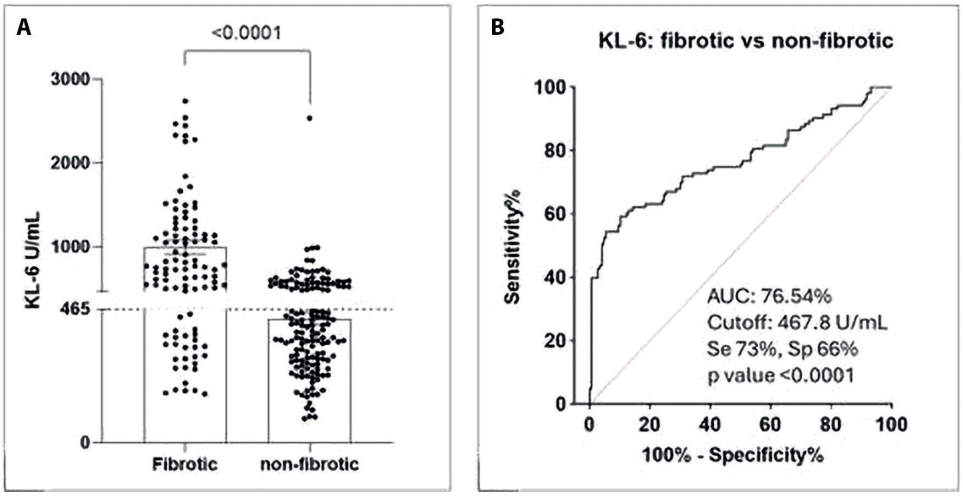

Figure 1. Serum KL-6 values in patients stratified according to pulmonary fibrosis. High KL-6 concentrations (a) were reported in fibrotic group (p<0.0001) with a cut-off value (b) of 467.8U/mL able to distinguish fibrotic than non-fibrotic patients (p<0.0001, sensitivity 73% and specificity 66%). *Abbreviations:* KL-6, Krebs von den Lungen-6; AUC, area under the curve.

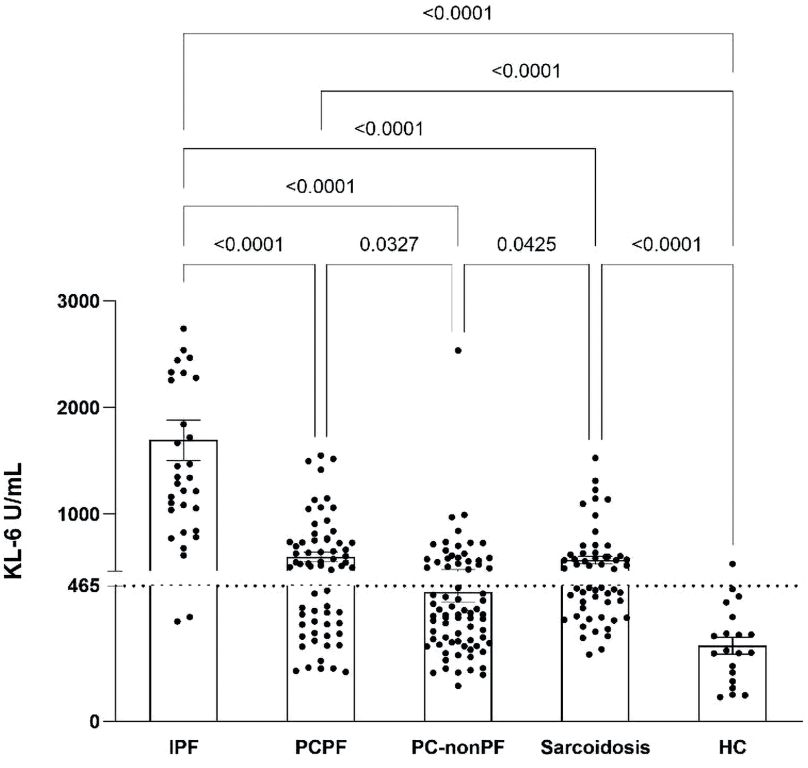

Figure 2. Serum KL-6 values in disease groups IPF, PCPF, PC-nonPF and sarcoidosis compared with healthy control (HC). Highest KL-6 concentrations were reported in IPF than other groups (p<0.0001), while the lowest one in HC group (p<0.0001). *Abbreviations:* IPF, idiopathic pulmonary fibrosis; PCPF, post-COVID19 pulmonary fibrosis; PC-nonPF, post-COVID19 without pulmonary fibrosis; KL-6, Krebs von den Lungen-6; FVC, forced vital capacity; DLco, diffusing capacity of the lungs for carbon monoxide.

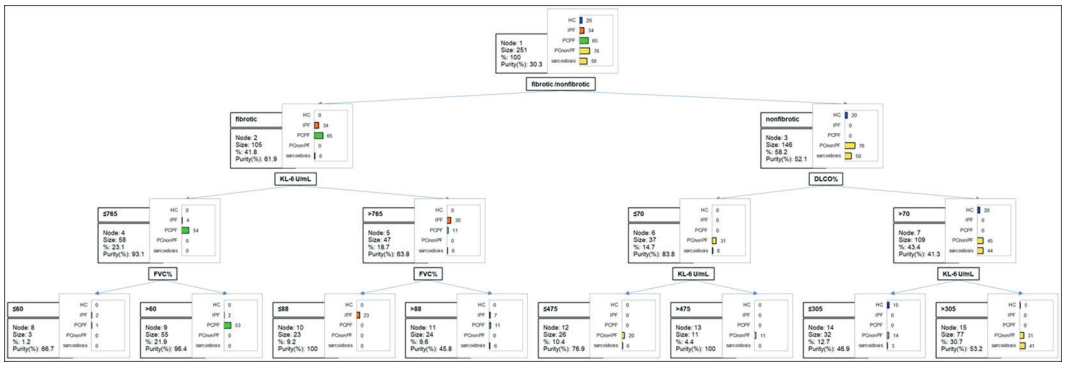

Figure 3. Decision tree model of fibrotic and non-fibrotic patients using KL-6 values, FVC% and DLco%. The model showed KL-6 >765U/mL and FVC ≤88% for 67% of IPF patients. KL-6 values ≤765U/mL and FVC >60% for 81% of PCPF patients. On the other hand, DLco >70% and KL-6 >305U/mL cluster for 82% of sarcoidosis patients. *Abbreviations:* IPF, idiopathic pulmonary fibrosis; PCPF, post-COVID19 pulmonary fibrosis; PC-nonPF, post-COVID19 without pulmonary fibrosis; KL-6, Krebs von den Lungen-6; FVC, forced vital capacity; DLco, diffusing capacity of the lungs for carbon monoxide.

concentrations cut-off values showed a classification for 67% of IPF patients with KL-6 >765U/mL and FVC ≤88%. 81% of PCPF patients were clustered with KL-6 ≤765U/mL and FVC >60%. On the other hand, DLco >70% and KL-6 >305U/mL cluster for 82% of sarcoidosis patients.

Stratifying PCPF and PC-nonPF patients according to request for IMV at hospital admission (Table s2), KL-6 concentrations tend to be higher in the subgroup of PCPF patients admitted in ICU for IMV (median (IQR), 546 (301, 737) U/mL) even if it did not reach statistical significance (p=0.18).

Discussion

This study validated the usefulness of KL-6 as a reliable marker for identifying fibrotic lung damages, both idiopathic and secondary to COVID19. Due to lung tissue damage and impaired gas exchange caused by SARS-CoV-2 infection, irreversible pulmonary fibrosis may develop in patients suffering COVID-19 (19). Furthermore, patients hospitalized with moderate COVID19 may develop post-acute pulmonary fibrosis (20). Consequently, early diagnosis and a prompt therapeutic assessment are essential to prevent irreversible deterioration in lung function. Biomarkers that reflect the underlying lung pathophysiology are increasingly valuable for assessing the severity of both COVID-19 and pulmonary fibrosis. KL-6 has been previously proposed as excellent diagnostic biomarker for detecting fibrotic ILD, which, regardless of the specific disease entity and extent of disease, is always elevated and is a reliable biomarker of lung fibrosis in various diseases (21). Stratifying our cohort in fibrotic and non-fibrotic patients, KL-6 concentrations were strongly suggestive of lung fibrosis with a cutoff value of 467.8 U/mL (sensitivity 73% and specificity 66%). This is probably related to the architectural distortion of lung parenchyma due to fibrogenesis and to the augmented permeability of alveolar capillary membrane induced by inflammation, which led to an increased release of KL-6 in the bloodstream. Our interest was aroused by the observation that this biomarker was correlated with prognosis in ILD, reflecting type I and type II alveolar pneumocyte damage. In PCPF patients, KL-6 concentrations at peripheral blood level can reflect severe interstitial lung damage, epithelial lung alterations and regenerative processes secondary to SARS-Cov-2 infection. In this context, a further aim was to perform KL-6 detection in the follow-up of SARS-CoV-2-induced interstitial pneumonia patients. Several authors demonstrated the usefulness of KL-6 for detecting disease severity and progression in COVID19 patients (22, 23, 11). In our previous study, we identified COVID19 patients who developed severe persistent fibrotic lung sequelae (n=14, 54%) at HRCT showed persistent high levels of KL-6 in the

follow-up, implicating that this biomarker may be useful in the mid-long-term management of these patients (22). To corroborate such findings, in the present study we enlarged the study population including 141 COVID19 patients of whom 65 had PCPF. In accordance with previous reports, KL-6 levels were elevated in PCPF patients compared to those with PC-nonPF and HC, further confirming the reliability of this biomarker to detect fibrotic alterations in COVID-19 patients. It should also be noted that KL-6 levels are not significantly elevated in patients undergoing IMV, indicating that IMV per se does not alter the values of this biomarker, thereby further supporting its reliability in detecting PCPF. In IPF patients, higher KL-6 concentrations were correlated with higher FEV1%, supporting the relationship between KL-6 elevation and impaired respiratory function in fibrotic lung disease. Though machine learning approach, we constructed a model to combine LFT parameters and KL-6 values for clustering fibrotic and non-fibrotic patients with an acceptable accuracy. In particular, the model showed a KL-6 cutoff value greater than 765 U/mL and FVC%≤88 for 67% of IPF patients. However, KL-6 values ≤765U/mL and FVC >60% cluster 81% of PCPF patients.

Conclusion

Increased serum KL-6 levels in patients with fibrotic interstitial lung disease (IPF and PCPF) reflect ongoing alveolar epithelial damage and the proliferative activity of type II pneumocytes. This supports the potential role of KL-6, combined with pulmonary function parameters, as a biomarker to assess the extent and severity of lung fibrosis. Our study proposed a good model for identifying lung fibrosis including KL-6 values and clinical background. In this context, combination of serum marker and clinical data, as seen in our cohort, may lead to a further improvement in diagnostic accuracy for pulmonary fibrosis, idiopathic and secondary to COVID19.

Author Contributions: M.d.A. made substantial contributions to the conception of the work. M.d.A., I.P., L.B. and S.B. made significant contributions to the data analysis and interpretation. M.d.A., P.C. and E.B. made significant contributions to the design of the work and the interpretation of data. M.d.A. and P.C. drafted the original manuscript. E.B. and other authors substantially contributed to the revision of the manuscript drafts. All authors have approved the submitted version of the manuscript and agreed to be accountable for any part of the work.

Institutional Review Board Statement: The study was approved by the regional ethical review board of Siena, Italy (C.E.A.V.S.E. approval number Markerlung17431; approval date 15/06/2020), and complied with the declaration of Helsinki.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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

Artificial Intelligence Involvement: The authors disclose that the material has not been produced with the help of any artificial intelligence software or tool.

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Appendix

Table S1. Demographic, clinical and functional data of patients stratified according to pulmonary fibrosis diagnosis.

Parameters	Fibrotic, n = 105	Non-fibrotic, n = 146	p values
Age, median (Q1, Q3) years	72 (64, 78)	59 (52, 70)	**<0.01**
Gender, n (%)			**<0.01**
Male	73 (70%)	74 (51%)	
Female	33 (30%)	72 (49%)	
BMI, median (Q1, Q3)	27.0 (24.7, 30.5)	28.3 (24.2, 32.1)	0.36
Diagnosis, n (%)			**<0.01**
post-COVID19	65 (62%)	76 (52%)	
sarcoidosis	6 (5.7%)	50 (34%)	
IPF	34 (32%)	0 (0%)	
HC	0 (0%)	20 (14%)	
KL-6 CLEIA, median (Q1, Q3)	751 (395, 1.226)	399 (288, 536)	**<0.01**
Lung function test parameters, median (Q1, Q3)			
DLCO%	66 (45, 79)	77 (65, 86)	**<0.01**
FVC%	89 (74, 104)	96 (85, 106)	**0.04**
FEV1%	95 (84, 107)	100 (88, 109)	0.17

Abbreviations: IPF, idiopathic pulmonary fibrosis; KL-6, Krebs von den Lungen-6; FVC, forced vital capacity; DLco, diffusing capacity of the lungs for carbon monoxide.; FEV1, forced expiratory volume in the first second.

Table S2. KL-6 concentrations in PCPF and PC-nonPF patients stratified according to request for IMV.

	Nonintubation PCPF N = 38	Nonintubation PCnonPF N = 70	IMV-PCPF N = 27	IMV-PCnonPF N = 6	p value
KL6 U/mL, median (Q1, Q3)	472 (304, 664)	399 (288, 574)	546 (301, 737)	305 (257, 381)	0.18

Abbreviations: IMV, invasive mechanical ventilation; PCPF, post-COVID19 pulmonary fibrosis; PC-nonPF, post-COVID19 without pulmonary fibrosis; KL-6, Krebs von den Lungen-6.