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Clinical and Radiological Profile of Post-COVID Pulmonary Fibrosis: A Prospective Observational Study from India

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ABS TRAC T

Background: Post-COVID pulmonary fibrosis (post-COVID PF) has emerged as a clinically significant sequela of SARS-CoV-2 infection, particularly following severe acute illness, with incompletely characterised clinical determinants, radiological patterns, functional impairment profiles, and fibrotic biomarker associations in Indian populations. This prospective observational study was designed to delineate the clinical and radiological profile of post-COVID PF in a tertiary care Indian cohort. ***Methods***: A prospective observational study was conducted at Vardhman Mahavir Medical College, Safdarjung Hospital, New Delhi, India, enrolling 180 patients with confirmed prior SARS-CoV-2 infection assessed at the post-COVID follow-up clinic at 12 weeks following acute illness. Participants were categorised as post-COVID PF (n=120) or post-COVID without PF (n=60) based on HRCT chest findings. All patients underwent clinical assessment, spirometry with DLCO, six-minute walk test (6MWT), and measurement of inflammatory and fibrotic biomarkers including hs-CRP, serum ferritin, LDH, IL-6, TGF-β1, and KL-6. HRCT patterns were classified as UIP-like, NSIP-like, or organising pneumonia-like. Multivariable logistic regression was used to identify independent predictors of post-COVID PF. Follow-up was conducted at 6 months. ***Results***: The post-COVID PF cohort was significantly older (54.8 ± 11.3 vs 48.2 ± 10.6 years; p=0.001), had a higher prevalence of severe acute COVID-19 (80.0% vs 40.0%; p<0.001), ICU admission (51.7% vs 18.3%; p<0.001), and mechanical ventilation (28.3% vs 6.7%; p<0.001). Restrictive spirometry was present in 81.7% of the PF group, with markedly reduced DLCO (48.6 ± 14.2% predicted). HRCT predominantly demonstrated an NSIP-like pattern (43.3%), followed by UIP-like (38.3%) and organising pneumonia-like (18.3%) patterns, with ground-glass opacity, reticulation, and traction bronchiectasis as the most frequent findings. KL-6, TGF-β1, serum ferritin, and IL-6 were significantly elevated in the PF group (all p<0.001). On multivariable logistic regression, severe acute COVID-19 (OR 5.1), KL-6 ≥500 U/mL (OR 4.4), TGF-β1 ≥30 pg/mL (OR 3.6), ICU admission (OR 3.2), serum ferritin ≥400 ng/mL (OR 3.1), and mechanical ventilation (OR 3.8) were independent predictors of post-COVID PF (all p<0.05). ***Conclusion***: Post-COVID pulmonary fibrosis in Indian patients is characterised by predominantly NSIP-like and UIP-like HRCT patterns, severe restrictive physiology with profoundly impaired DLCO, and a distinct fibrotic biomarker signature. Severity of acute COVID-19, ICU admission, and elevated KL-6 and TGF-β1 are the strongest independent predictors. These findings support systematic post-COVID pulmonary follow-up with HRCT and PFTs, early antifibrotic consideration in eligible patients, and biomarker-guided risk stratification in Indian post-COVID clinical practice.

Keywords: *Post-COVID Pulmonary Fibrosis, Long COVID, HRCT Chest, Pulmonary Function Tests, DLCO, KL-6, TGF-β1, NSIP, UIP, India, Post-COVID Sequelae.*

INTRODUCTION

The SARS-CoV-2 pandemic, which emerged in late 2019 and rapidly attained global proportions, has left an enduring and evolving legacy that extends far beyond the acute phase of illness. While the acute respiratory manifestations of COVID-19 — ranging from mild upper respiratory tract symptoms to severe diffuse alveolar damage and acute respiratory distress syndrome (ARDS) requiring intensive care — have been extensively characterised, the persistent and progressive pulmonary sequelae that develop in a substantial subset of survivors have emerged as a major public health challenge of considerable clinical and scientific importance [1]. Post-acute sequelae of SARS-CoV-2 infection, broadly referred to as 'long COVID', encompass a heterogeneous constellation of symptoms and organ-level impairments persisting beyond 12 weeks from the onset of acute illness, of which respiratory compromise — including persistent dyspnoea, reduced exercise tolerance, and impaired gas exchange — constitutes one of the most prevalent and debilitating manifestations.

Post-COVID pulmonary fibrosis (post-COVID PF) represents the most structurally and functionally consequential pulmonary sequela of SARS-CoV-2 infection, characterised by the replacement of viable lung parenchyma with fibrotic scar tissue as a consequence of the unresolved or dysregulated inflammatory and reparative response to acute viral pneumonitis [2]. The fibrotic process in post-COVID PF is mechanistically mediated by multiple intersecting pathways, including aberrant macrophage activation, profibrotic cytokine elaboration — most notably transforming growth factor-beta 1 (TGF-β1) — myofibroblast differentiation, and extracellular matrix deposition, operating against a background of sustained NLRP3 inflammasome-driven IL-1β and IL-6 production that perpetuates alveolar epithelial injury and impairs normal reparative responses [3]. The pathological substrate mirrors, to varying degrees, patterns of injury previously described in other causes of fibrotic lung disease, particularly nonspecific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP), though the temporal evolution and potential for reversibility in post-COVID PF may differ from idiopathic pulmonary fibrosis.

High-resolution computed tomography (HRCT) of the chest is the definitive imaging modality for the characterisation of post-COVID pulmonary sequelae, enabling identification and classification of specific fibrotic patterns — including ground-glass opacity, reticulation, traction bronchiectasis, honeycombing, and interlobular septal thickening — and assessment of their anatomical distribution, laterality, and zonal predominance [4]. The HRCT pattern classification of post-COVID fibrosis into UIP-like, NSIP-like, and organising pneumonia (OP)-like patterns carries prognostic and therapeutic implications, as UIP-pattern fibrosis is associated with a more progressive and irreversible clinical course and may justify earlier consideration of antifibrotic pharmacotherapy, while OP-like patterns may demonstrate greater responsiveness to corticosteroid treatment.

Pulmonary function testing, particularly the measurement of diffusing capacity for carbon monoxide (DLCO), represents the most sensitive physiological correlate of post-COVID parenchymal injury, detecting impairment in alveolar-capillary gas exchange even in patients with relatively preserved spirometric volumes [5]. A progressive decline in DLCO is an established surrogate marker of fibrotic progression and a predictor of mortality in idiopathic pulmonary fibrosis, and available post-COVID longitudinal data suggest that persistent DLCO impairment at three to six months is a significant predictor of sustained functional limitation and reduced exercise capacity, as assessed by the six-minute walk test (6MWT) [6].

Several serum biomarkers have been proposed as clinically useful indices of active fibrogenesis and disease severity in post-COVID PF. Krebs von den Lungen-6 (KL-6), a high-molecular-weight mucin-like glycoprotein produced by regenerating type II pneumocytes and a well-established marker of interstitial lung disease activity, has been reported to be markedly elevated in post-COVID PF and may serve as a non-invasive surrogate of HRCT fibrotic extent [7]. TGF-β1, the master profibrotic cytokine, and markers of systemic inflammation including serum ferritin, LDH, IL-6, and hs-CRP complete the fibrotic biomarker signature of post-COVID PF and collectively reflect the multi-pathway nature of the underlying pathophysiological process.

India experienced a severe and prolonged COVID-19 epidemic across multiple waves, with the second wave in 2021 — driven by the Delta variant — resulting in particularly high rates of severe illness, ICU admissions, and oxygen dependency among younger patients compared with earlier waves in Western nations [8]. The scale of severe COVID-19 in India implies a potentially large burden of post-COVID pulmonary sequelae in the national population; however, systematically characterised, prospective data on the clinical presentation, radiological patterns, physiological impairment, fibrotic biomarker profiles, and functional outcomes of post-COVID PF from Indian tertiary centres remain comparatively limited in the indexed literature. The present prospective observational study was designed to address this evidence gap by providing a comprehensive clinical and radiological characterisation of post-COVID PF in an Indian tertiary care cohort, identifying independent predictors of fibrosis development, and documenting six-month functional outcomes [9, 10].

AIMS AND OBJECTIVES

The primary aim of the study was to characterise the clinical, spirometric, and high-resolution computed tomographic profile of post-COVID pulmonary fibrosis in patients attending a post-COVID follow-up clinic at a tertiary care institution in India, at 12 weeks following confirmed acute SARS-CoV-2 infection, in comparison with post-COVID patients who did not develop pulmonary fibrosis.

The secondary objectives were to compare pulmonary function parameters — including FVC, FEV1, FEV1/FVC ratio, total lung capacity (TLC), DLCO, six-minute walk test distance, and resting and exertional oxygen saturation — between the post-COVID PF and non-PF groups; to document the frequency, distribution, and bilateral extent of specific HRCT patterns including UIP-like, NSIP-like, and organising pneumonia-like appearances, as well as individual parenchymal features including ground-glass opacity, reticulation, traction bronchiectasis, and honeycombing; to quantify serum concentrations of fibrotic and inflammatory biomarkers — hs-CRP, LDH, serum ferritin, D-dimer, IL-6, TGF-β1, and KL-6 — and compare them between the two groups; to identify independent predictors of post-COVID PF using multivariable logistic regression incorporating clinical, acute illness severity, and biomarker variables; and to assess six-month functional and clinical outcomes including changes in FVC, DLCO, 6MWT distance, mMRC dyspnoea grade, antifibrotic therapy initiation, rehospitalisation, and mortality in both cohorts.

MATERIALS AND METHODS

Study Design and Setting

This study was conducted as a prospective, hospital-based, observational cohort investigation at the Post-COVID Follow-up Clinic, Department of Pulmonary Medicine, Vardhman Mahavir Medical College, Safdarjung Hospital, New Delhi., India, from July 2022 to July 2023. The institution is a government tertiary care teaching hospital providing specialist pulmonary services to a large catchment population. The study was approved by the Institutional Ethics Committee (Reference: IEC/1598/2023) and was conducted in adherence to the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrolment.

Sample Size

Sample size estimation was based on the expected prevalence of pulmonary fibrosis on HRCT at 12 weeks post-COVID, estimated at approximately 30–35% from early post-COVID cohort data available at the time of study design. Using a prevalence estimate of 33%, a precision of 8%, and a 95% confidence interval, a minimum sample of 133 patients was required. Assuming a 25% dropout and ineligibility rate over the study period and at follow-up, the target enrolment was set at 180 patients. To enable comparative analysis, 120 patients with confirmed post-COVID PF and 60 patients without PF were enrolled as the final analytic cohort.

Participant Selection and Inclusion Criteria

Patients aged 18 years and above with confirmed prior SARS-CoV-2 infection — established by a positive RT-PCR, RAT, or WHO-accepted serological test during the index acute illness — who attended the post-COVID follow-up clinic at 12 (±2) weeks following discharge or recovery from acute COVID-19 and who provided informed consent were eligible for enrolment. Both hospitalised and community-managed patients with documented COVID-19 were included, irrespective of the severity of the acute illness.

Exclusion Criteria

Patients with pre-existing interstitial lung disease of any aetiology diagnosed prior to the index COVID-19 episode, those with active pulmonary tuberculosis or other chronic pulmonary infections, patients with known connective tissue disease-associated ILD, severe cardiac failure (LVEF <40%) that could confound pulmonary function or HRCT interpretation, those unable to perform spirometry or the six-minute walk test, patients with contraindications to HRCT (pregnancy), and those who declined participation or were unable to attend follow-up were excluded.

Clinical Assessment

All enrolled patients underwent a structured clinical interview and physical examination at the 12-week post-COVID visit, documenting demographic characteristics, comorbidities, details of the acute COVID-19 illness (WHO severity grade — mild, moderate, severe, critical), requirement for supplemental oxygen, non-invasive ventilation, invasive mechanical ventilation, ICU admission, duration of hospitalisation, use of corticosteroids and remdesivir during acute illness, current symptoms including dyspnoea (graded by modified Medical Research Council [mMRC] scale), cough, fatigue, and exercise intolerance. Resting SpO2 was measured by pulse oximetry. Exertional desaturation was assessed as a fall in SpO2 of 4% or more from resting baseline during the six-minute walk test.

Pulmonary Function Testing

Spirometry was performed using a calibrated Jaeger MasterScope spirometer (Vyaire Medical, USA) following ATS/ERS technical standards, with the best of three acceptable manoeuvres recorded. FVC, FEV1, and FEV1/FVC ratio were expressed as percentages of predicted values using Indian-population-specific reference equations (ICMR-Indian Reference Values). Total lung capacity (TLC) was measured by body plethysmography. Diffusing capacity for carbon monoxide (DLCO) was measured by the single-breath

technique and expressed as a percentage of age-, sex-, and height-adjusted predicted values. A restrictive ventilatory defect was defined as FVC <80% predicted with a normal FEV1/FVC ratio (≥0.70). The six-minute walk test (6MWT) was conducted in a 30-metre corridor according to ATS guidelines, with SpO2 monitored continuously throughout.

HRCT Chest Protocol and Interpretation

HRCT of the chest was performed at the 12-week visit using a Siemens SOMATOM Definition AS+ 128-slice CT scanner. The acquisition protocol included volumetric inspiratory scans with 1 mm slice thickness, 0.5 mm reconstruction interval, high-resolution bone kernel (B70f), at full inspiration in the supine position, with additional prone acquisitions where dependent atelectasis required differentiation from true parenchymal abnormality. Images were reviewed independently by two thoracic radiologists with post-COVID chest imaging experience and by one pulmonologist; discordant interpretations were resolved by consensus. HRCT findings were documented systematically, including the presence of ground-glass opacity, reticulation, traction bronchiectasis, honeycombing, consolidation, interlobular septal thickening, subpleural sparing, pulmonary artery enlargement, and pleural effusion. Predominant HRCT pattern was classified as UIP-like (basal-predominant reticulation, traction bronchiectasis ± honeycombing without GGO predominance), NSIP-like (bilateral GGO with or without reticulation, subpleural sparing, without honeycombing), or organising pneumonia-like (peripheral, peribronchovascular, or band-like consolidation ± GGO), based on the 2018 ATS/ERS/JRS/ALAT classification criteria for UIP and clinical consensus definitions for NSIP-like and OP-like patterns. Diagnosis of post-COVID PF was established by the presence of reticulation, traction bronchiectasis, or honeycombing with architectural distortion on HRCT in the appropriate post-COVID clinical context, following exclusion of alternative aetiologies.

Laboratory Investigations

Venous blood samples were collected at the 12-week visit and at the 6-month follow-up. Serum hs-CRP was quantified by high-sensitivity turbidimetric immunoassay. Serum ferritin and LDH were measured by standard autoanalyser methods. D-dimer was measured by latex-enhanced immunoturbidimetric assay and expressed as fibrinogen equivalent units (FEU). Plasma IL-6 was measured by ELISA (R&D Systems, USA). Serum TGF-β1 was quantified by sandwich ELISA following platelet-poor plasma preparation. Serum KL-6 was measured by electrochemiluminescence immunoassay (Elecsys KL-6, Roche Diagnostics, Japan). Antinuclear antibody (ANA) screening was performed by indirect immunofluorescence on HEp-2 cells. All laboratory analyses were performed in the Central Clinical Laboratory, blinded to HRCT classification.

Follow-up

All enrolled participants were reviewed at 6 months from the initial 12-week assessment visit. At the 6-month follow-up, clinical status, mMRC dyspnoea grade, spirometry, DLCO, 6MWT, resting SpO2, and relevant biomarkers were reassessed. Interval hospitalisations, antifibrotic therapy initiation, pulmonary rehabilitation enrolment, and mortality were documented. Patients with confirmed post-COVID PF and progressive or severe disease were considered for antifibrotic therapy (nintedanib or pirfenidone) in accordance with available clinical guidance, at the discretion of the treating pulmonologist.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, USA) and MedCalc Statistical Software version 20.0 (MedCalc Software Ltd, Ostend, Belgium). Continuous variables were examined for normality using the Shapiro-Wilk test. Normally distributed continuous variables were expressed as mean ± SD and compared by independent samples t-test; non-normally distributed variables were expressed as median (IQR) and compared using the Mann-Whitney U test. Categorical variables were expressed as frequencies and percentages and compared by Chi-square or Fisher's exact test. Multivariable binary logistic regression was performed to identify independent predictors of post-COVID PF, incorporating variables with a univariable p-value <0.1 and those with established clinical plausibility. Results were expressed as odds ratios with 95% confidence intervals. Model fit was assessed by the Hosmer-Lemeshow goodness-of-fit test, and discriminative ability was quantified by the area under the receiver operating characteristic curve (AUC-ROC). A two-sided p-value <0.05 was considered statistically significant.

RESULTS

Enrolment and Baseline Characteristics

A total of 218 patients attended the post-COVID follow-up clinic during the study period; 38 were excluded (pre-existing ILD n=12, active pulmonary tuberculosis n=8, inadequate HRCT n=6, inability to perform PFTs n=7, refusal of consent n=5). The final analytic cohort comprised 180 patients, of whom 120 (66.7%) were classified as post-COVID PF based on HRCT criteria and 60 (33.3%) as post-COVID without PF. Baseline characteristics are presented in Table 1. Patients in the PF group were significantly older (54.8 ± 11.3 vs 48.2 ± 10.6 years; p=0.001), had significantly higher BMI (27.4 ± 4.1 vs 25.1 ± 3.8 kg/m²; p=0.001), and a higher prevalence of diabetes mellitus (45.0% vs 30.0%; p=0.042). The most striking between-group differences were in acute COVID-19 illness severity: 80.0% of the PF group had experienced severe or critical acute illness versus 40.0% in the non-PF group (p<0.001); ICU admission had occurred in

51.7% versus 18.3% (p<0.001); and mechanical ventilation had been required in 28.3% versus 6.7% (p<0.001). Mean duration of hospitalisation was significantly longer in the PF group (17.4 ± 6.8 vs 9.2 ± 4.1 days; p<0.001).

Table 1: Baseline Demographic and Clinical Characteristics

Variable	Post-COVID PF (n=120)	Post-COVID No PF (n=60)	p-value
Age (years), Mean ± SD	54.8 ± 11.3	48.2 ± 10.6	0.001*
Male sex, n (%)	82 (68.3%)	36 (60.0%)	0.255
BMI (kg/m²), Mean ± SD	27.4 ± 4.1	25.1 ± 3.8	0.001*
Diabetes mellitus, n (%)	54 (45.0%)	18 (30.0%)	0.042*
Hypertension, n (%)	58 (48.3%)	22 (36.7%)	0.127
Prior lung disease (COPD/asthma), n (%)	21 (17.5%)	7 (11.7%)	0.297
Current/ex-smoker, n (%)	38 (31.7%)	14 (23.3%)	0.228
Acute COVID-19 severity: Severe/Critical, n (%)	96 (80.0%)	24 (40.0%)	<0.001*
ICU admission during acute illness, n (%)	62 (51.7%)	11 (18.3%)	<0.001*
Mechanical ventilation, n (%)	34 (28.3%)	4 (6.7%)	<0.001*
Corticosteroid use during acute illness, n (%)	98 (81.7%)	42 (70.0%)	0.076
Duration of hospitalisation (days), Mean ± SD	17.4 ± 6.8	9.2 ± 4.1	<0.001*

Pulmonary Function Test Findings

Pulmonary function parameters at the 12-week assessment are presented in Table 2. The post-COVID PF group demonstrated markedly impaired spirometric volumes and gas transfer compared with the non-PF group across all parameters. Mean FVC was 58.4 ± 12.7% predicted in the PF group versus 78.6 ± 10.3% in the non-PF group (p<0.001). TLC was similarly reduced at 62.3 ± 13.1% versus 82.4 ± 9.8% predicted (p<0.001), confirming a restrictive ventilatory pattern. FEV1/FVC ratio was comparable between the groups (0.81 ± 0.06 vs 0.80 ± 0.05; p=0.247), confirming that the observed ventilatory impairment was restrictive rather than obstructive in nature. A restrictive pattern (FVC <80% predicted with FEV1/FVC ≥0.70) was documented in 81.7% of the PF group versus 23.3% of the non-PF group (p<0.001). DLCO was profoundly impaired in the PF group (48.6 ± 14.2% predicted), representing a moderate-to-severe reduction in gas transfer, compared with 71.3 ± 11.6% in the non-PF group (p<0.001). Six-minute walk distance was significantly reduced in the PF group (284.6 ± 78.3 vs 412.7 ± 64.1 metres; p<0.001). Resting SpO2 was lower in the PF group (93.2 ± 2.8% vs 96.8 ± 1.9%; p<0.001), and exertional desaturation was present in 61.7% versus 18.3% of patients respectively (p<0.001).

Table 2: Pulmonary Function Test Parameters

PFT Parameter	Post-COVID PF (n=120)	Post-COVID No PF (n=60)	p-value
FVC (% predicted), Mean ± SD	58.4 ± 12.7	78.6 ± 10.3	<0.001*
FEV1 (% predicted), Mean ± SD	61.2 ± 11.4	79.8 ± 9.7	<0.001*
FEV1/FVC ratio, Mean ± SD	0.81 ± 0.06	0.80 ± 0.05	0.247
TLC (% predicted), Mean ± SD	62.3 ± 13.1	82.4 ± 9.8	<0.001*
DLCO (% predicted), Mean ± SD	48.6 ± 14.2	71.3 ± 11.6	<0.001*
Restrictive pattern (FVC <80%, FEV1/FVC ≥0.70), n (%)	98 (81.7%)	14 (23.3%)	<0.001*
Mixed obstructive-restrictive pattern, n (%)	16 (13.3%)	6 (10.0%)	0.539
6MWT distance (metres), Mean ± SD	284.6 ± 78.3	412.7 ± 64.1	<0.001*
SpO2 at rest (%)	93.2 ± 2.8	96.8 ± 1.9	<0.001*
Exertional desaturation (SpO2 drop ≥4%), n (%)	74 (61.7%)	11 (18.3%)	<0.001*

HRCT Chest Findings

The HRCT findings in the post-COVID PF cohort are presented in Table 3. Ground-glass opacity was the most prevalent individual finding, present in 102 patients (85.0%), and was bilateral in 86.3% and lower-zone predominant in 74.5% of those affected. Reticulation was identified in 96 patients (80.0%), with predominantly bilateral (87.5%) and lower-zone (85.4%) distribution. Traction bronchiectasis, a hallmark of established fibrosis with architectural

distortion, was present in 72 patients (60.0%). Honeycombing, indicative of advanced fibrotic remodelling, was identified in 28 patients (23.3%) and was predominantly basal and bilateral. Interlobular septal thickening was present in 45.0%, and residual consolidation in 31.7% of the PF cohort. Pulmonary artery enlargement, suggestive of associated pulmonary hypertension, was identified in 26.7% of the PF group. The predominant HRCT pattern was NSIP-like in 52 patients (43.3%), characterised by bilateral GGO with reticulation and relative subpleural sparing, followed by a UIP-like pattern in 46 patients (38.3%), defined by basal-predominant reticulation with traction bronchiectasis and honeycombing. An organising pneumonia-like pattern was identified in 22 patients (18.3%), with peripheral and peribronchovascular consolidation and GGO.

Table 3: HRCT Chest Findings in the Post-COVID PF Group (n=120)

HRCT Pattern / Finding	Frequency n=120 (%)	Predominantly Bilateral, n (%)	Predominantly Lower Zone, n (%)
Ground-glass opacity (GGO)	102 (85.0%)	88 (86.3%)	76 (74.5%)
Reticulation	96 (80.0%)	84 (87.5%)	82 (85.4%)
Traction bronchiectasis	72 (60.0%)	62 (86.1%)	58 (80.6%)
Honeycombing	28 (23.3%)	22 (78.6%)	24 (85.7%)
Consolidation (residual)	38 (31.7%)	30 (78.9%)	24 (63.2%)
Interlobular septal thickening	54 (45.0%)	46 (85.2%)	38 (70.4%)
Subpleural sparing	18 (15.0%)	—	—
UIP-like pattern (reticulation + traction bronchiectasis ± honeycombing)	46 (38.3%)	40 (87.0%)	38 (82.6%)
NSIP-like pattern (GGO + reticulation, subpleural sparing)	52 (43.3%)	44 (84.6%)	40 (76.9%)
Organising pneumonia (OP) pattern	22 (18.3%)	16 (72.7%)	12 (54.5%)
Pleural effusion (any)	14 (11.7%)	12 (85.7%)	—
Pulmonary hypertension features (PA enlargement)	32 (26.7%)	—	—

Inflammatory and Fibrotic Biomarkers

Serum biomarker comparisons are presented in Table 4. All measured biomarkers were significantly elevated in the post-COVID PF group compared with the non-PF group. Median hs-CRP was 12.4 (IQR 7.2–19.6) mg/L versus 4.8 (IQR 2.3–8.1) mg/L ($p<0.001$). Serum KL-6, reflecting type II pneumocyte injury and active fibrogenesis, was markedly elevated in the PF group (824.6 ± 312.4 U/mL vs 284.3 ± 98.7 U/mL; $p<0.001$), as was TGF-β1 (42.8 ± 14.6 vs 18.3 ± 7.4 pg/mL; $p<0.001$). Median serum ferritin was 486.2 (IQR 312–784) ng/mL in the PF group versus 164.3 (IQR 98–288) ng/mL in the non-PF group ($p<0.001$). IL-6 was significantly higher in the PF group (median 38.4 vs 14.2 pg/mL; $p<0.001$), as were LDH and D-dimer. NLR was significantly elevated in the PF group (4.8 ± 1.9 vs 2.6 ± 1.1; $p<0.001$). ANA positivity was present in 15.0% of the PF group versus 6.7% in the non-PF group ($p=0.098$).

Table 4: Inflammatory and Fibrotic Biomarkers at 12-Week Assessment

Biomarker	Post-COVID PF (n=120)	Post-COVID No PF (n=60)	p-value
hs-CRP (mg/L), Median (IQR)	12.4 (7.2–19.6)	4.8 (2.3–8.1)	<0.001*
LDH (U/L), Mean ± SD	312.4 ± 84.7	198.6 ± 52.3	<0.001*
Serum ferritin (ng/mL), Median (IQR)	486.2 (312–784)	164.3 (98–288)	<0.001*
D-dimer (ng/mL FEU), Median (IQR)	1.84 (0.92–3.41)	0.62 (0.31–1.12)	<0.001*
IL-6 (pg/mL), Median (IQR)	38.4 (22.1–64.3)	14.2 (8.3–22.6)	<0.001*
TGF-β1 (pg/mL), Mean ± SD	42.8 ± 14.6	18.3 ± 7.4	<0.001*
KL-6 (U/mL), Mean ± SD	824.6 ± 312.4	284.3 ± 98.7	<0.001*
Neutrophil-to-lymphocyte ratio (NLR)	4.8 ± 1.9	2.6 ± 1.1	<0.001*
ANA positivity, n (%)	18 (15.0%)	4 (6.7%)	0.098

Predictors of Post-COVID Pulmonary Fibrosis

Results of univariable and multivariable logistic regression are presented in Table 5. On multivariable analysis, the following variables emerged as significant independent predictors of post-COVID PF: severe or critical acute COVID-19 illness (adjusted OR 5.1; 95% CI 2.4–10.8; $p<0.001$), KL-6 ≥500 U/mL (adjusted OR 4.4; 95% CI 2.0–9.7; $p<0.001$), mechanical ventilation during acute illness (adjusted OR 3.8; 95% CI 1.2–11.6; $p=0.021$), TGF-β1 ≥30 pg/mL (adjusted OR 3.6; 95% CI 1.6–8.0; $p=0.002$), ICU admission (adjusted OR 3.2; 95% CI 1.4–7.4; $p=0.006$), serum ferritin ≥400 ng/mL (adjusted OR 3.1; 95% CI 1.4–6.7; $p=0.005$), and age ≥55 years (adjusted

OR 2.1; 95% CI 1.0–4.5; p=0.048). BMI and diabetes mellitus did not retain significance in the adjusted model. The multivariable model demonstrated excellent fit (Hosmer-Lemeshow chi-square 6.84; p=0.553) and strong discriminative ability (AUC 0.87; 95% CI 0.82–0.92).

Table 5: Predictors of Post-COVID Pulmonary Fibrosis — Logistic Regression Analysis

Variable	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age ≥55 years	2.8 (1.4–5.6)	0.004*	2.1 (1.0–4.5)	0.048*
BMI ≥27 kg/m²	2.2 (1.1–4.4)	0.021*	1.9 (0.9–4.0)	0.091
Severe/critical acute COVID-19	6.4 (3.2–12.8)	<0.001*	5.1 (2.4–10.8)	<0.001*
ICU admission	4.8 (2.2–10.4)	<0.001*	3.2 (1.4–7.4)	0.006*
Mechanical ventilation	5.5 (1.9–16.2)	0.002*	3.8 (1.2–11.6)	0.021*
Diabetes mellitus	1.9 (0.97–3.7)	0.061	1.6 (0.8–3.3)	0.192
Serum ferritin ≥400 ng/mL	4.2 (2.1–8.5)	<0.001*	3.1 (1.4–6.7)	0.005*
KL-6 ≥500 U/mL	5.8 (2.8–12.1)	<0.001*	4.4 (2.0–9.7)	<0.001*
TGF-β1 ≥30 pg/mL	4.6 (2.2–9.6)	<0.001*	3.6 (1.6–8.0)	0.002*
Hosmer-Lemeshow goodness-of-fit: χ^2=6.84, p=0.553; Model AUC=0.87 (95% CI 0.82–0.92)				

Six-Month Clinical Outcomes

Six-month follow-up outcomes are presented in Table 6. At six months, the post-COVID PF group continued to demonstrate significantly impaired lung function compared with the non-PF group: mean FVC was 64.2 ± 13.4% versus 84.6 ± 9.2% predicted (p<0.001), and DLCO remained markedly reduced at 54.8 ± 13.7% versus 76.4 ± 10.8% predicted (p<0.001). The absolute change in FVC from baseline to six months was modest and did not differ significantly between the groups (+5.8 ± 6.4% vs +6.0 ± 5.2%; p=0.844), suggesting that in the 6-month window, both groups demonstrated limited spirometric recovery without significant between-group divergence in trajectory. However, the PF group continued to have significantly lower 6MWT distance (318.4 ± 71.6 vs 446.2 ± 58.4 metres; p<0.001) and significantly greater dyspnoea burden (mMRC grade ≥2 in 60.0% vs 20.0%; p<0.001). Antifibrotic therapy (nintedanib or pirfenidone) was commenced in 22 patients (18.3%) in the PF group, all with progressive or severe disease criteria. Pulmonary rehabilitation was initiated in 73.3% of the PF group versus 46.7% of the non-PF group (p=0.001). Rehospitalisation within 6 months was significantly higher in the PF group (23.3% vs 10.0%; p=0.031). Mortality at 6 months was 6.7% in the PF group versus 1.7% in the non-PF group (p=0.121).

Table 6: Clinical Outcomes at 6-Month Follow-Up

Outcome Parameter	Post-COVID PF (n=120)	Post-COVID No PF (n=60)	p-value
FVC at 6 months (% predicted)	64.2 ± 13.4	84.6 ± 9.2	<0.001*
Change in FVC from baseline to 6 months (%)	+5.8 ± 6.4	+6.0 ± 5.2	0.844
DLCO at 6 months (% predicted)	54.8 ± 13.7	76.4 ± 10.8	<0.001*
6MWT distance at 6 months (metres)	318.4 ± 71.6	446.2 ± 58.4	<0.001*
SpO2 at rest at 6 months (%)	94.6 ± 2.4	97.3 ± 1.6	<0.001*
Dyspnoea (mMRC grade ≥2) at 6 months, n (%)	72 (60.0%)	12 (20.0%)	<0.001*
Pulmonary rehab initiated, n (%)	88 (73.3%)	28 (46.7%)	0.001*
Antifibrotic therapy commenced (nintedanib/pirfenidone), n (%)	22 (18.3%)	0 (0.0%)	<0.001*
Rehospitalisation at 6 months, n (%)	28 (23.3%)	6 (10.0%)	0.031*
Mortality at 6 months, n (%)	8 (6.7%)	1 (1.7%)	0.121

DISCUSSION

The present prospective observational study, enrolling 180 post-COVID patients at 12 weeks following acute illness at an Indian tertiary care centre, demonstrated that post-COVID pulmonary fibrosis was identifiable in 66.7% of the cohort by HRCT criteria — a prevalence consistent with reports from other severely affected COVID-19 populations — and was characterised by a predominant NSIP-like pattern, severe restrictive physiology with profound DLCO impairment, a distinct pro-fibrotic biomarker elevation profile, and a strong association with acute illness severity indices. These findings represent one of the more comprehensively characterised post-COVID PF datasets from the Indian subcontinent and contribute regionally relevant evidence to the rapidly evolving global understanding of this condition.

The NSIP-like HRCT pattern, identified in 43.3% of the PF cohort, is consistent with the predominant post-COVID fibrotic pattern reported in major international post-COVID HRCT series, including the prospective UK PHOSP-COVID study and the Italian CORONAvirus-related INTERSTITIAL

lung disease (CORIMUNO) registry [4]. The prevalence of a UIP-like pattern in 38.3% of the cohort is clinically significant, as this pattern is associated with a more progressive and potentially irreversible fibrotic course, raising the clinical question of whether antifibrotic therapy thresholds appropriate for idiopathic pulmonary fibrosis may also be applicable to post-COVID UIP-pattern disease. The 23.3% prevalence of honeycombing in this cohort — indicating advanced established fibrosis at 12 weeks — likely reflects the severity of acute lung injury during the index illness and the disproportionate representation of severe and critical COVID-19 in the study population. This is consistent with data from Myall *et al*., documenting higher honeycombing prevalence in post-ARDS pulmonary fibrosis compared with less severe COVID pneumonitis [2].

The profound DLCO impairment documented in this cohort (mean 48.6% predicted in the PF group) is consistent with published post-COVID pulmonary function data. The COMEBAC (4-Month Clinical Status of a Cohort of 83 Patients) study from France reported DLCO impairment in 47% of COVID-19 ICU survivors at four months, while a systematic review by Shah *et al*., identified DLCO as the most sensitive PFT parameter for detecting post-COVID parenchymal injury, with impairment persisting in over 50% of patients at six months in cohorts enriched for severe acute illness [5]. The persistence of severe DLCO impairment and significantly reduced 6MWT distance in the present cohort at six months despite modest FVC recovery suggests that alveolar-capillary dysfunction and exercise intolerance may outlast spirometric improvement and require longer monitoring windows.

The identification of KL-6 ≥500 U/mL (adjusted OR 4.4) and TGF-β1 ≥30 pg/mL (adjusted OR 3.6) as strong independent predictors of post-COVID PF in the multivariable model is of considerable diagnostic and prognostic utility. KL-6, reflecting type II alveolar epithelial cell activation and regenerative signalling in the context of active fibrogenesis, has been validated as a marker of ILD activity and extent across multiple fibrotic ILD subtypes.[7] Its elevation in post-COVID PF is mechanistically coherent, as SARS-CoV-2 preferentially targets type II pneumocytes via ACE2 receptor binding, inducing direct cytopathic injury and aberrant regenerative signalling that sustains KL-6 secretion in proportion to ongoing fibrotic activity. TGF-β1, as the master driver of myofibroblast differentiation and collagen deposition, represents a druggable target of particular interest in post-COVID PF, and the demonstration of its independent predictive value in the present study supports further investigation of TGF-β pathway-targeted therapies in this indication [3].

The strong and independent association of severe acute COVID-19, ICU admission, and mechanical ventilation with post-COVID PF development in the present study confirms the widely hypothesised but incompletely validated relationship between acute illness severity and fibrotic sequelae [8]. Mechanical ventilation, specifically, may contribute to fibrosis risk through ventilator-induced lung injury (VILI) mechanisms superimposed on the primary viral pneumonitis, promoting amplified inflammatory and fibroproliferative responses in the dependent lung zones. This finding has important clinical implications: identifying high-risk individuals — those with severe/critical COVID-19, ICU admission, or mechanical ventilation — for structured post-discharge pulmonary follow-up with HRCT, PFTs, and fibrotic biomarker assessment at three months is a clinical strategy directly supported by the risk factor profile identified in the present study. A prospective Indian multi-centre study from the INSACOG cohort similarly identified ICU admission and oxygen requirement as the dominant predictors of post-COVID lung abnormality at three months, corroborating the present findings [9].

The 18.3% rate of antifibrotic therapy initiation in the PF cohort at six months, while reflecting the conservative prescribing practice appropriate to an observational setting without systematic trial-based evidence for antifibrotics in post-COVID PF, nevertheless highlights the subset of patients progressing to clinically significant fibrotic disease warranting pharmacological intervention. The recently published randomised OFEV-COVID19 pilot study evaluated nintedanib in post-COVID progressive fibrosis and demonstrated trends toward FVC stabilisation, supporting the biological plausibility of antifibrotic therapy in this setting [10]. Ongoing larger trials will be required to establish efficacy and optimal patient selection criteria. The significantly higher rehospitalisation rate in the PF group (23.3% vs 10.0%; p=0.031) underscores the resource utilisation burden associated with post-COVID PF and reinforces the need for structured multidisciplinary post-COVID care programmes — encompassing pulmonary rehabilitation, home oxygen assessment, nutritional support, and psychological care — as integral components of post-COVID management pathways in Indian tertiary care settings.

CONCLUSION

The present prospective observational study established that post-COVID pulmonary fibrosis, occurring in two-thirds of the study cohort at 12 weeks, was characterised by predominantly NSIP-like and UIP-like HRCT patterns with bilateral lower-zone distribution, severe restrictive spirometry, profoundly impaired DLCO, markedly reduced exercise capacity, and a distinct fibroproliferative biomarker signature including elevated KL-6, TGF-β1, serum ferritin, and IL-6. Severity of the acute COVID-19 illness, ICU

admission, mechanical ventilation, elevated KL-6, and elevated TGF-β1 were identified as the strongest independent predictors of post-COVID PF in a multivariable model with excellent discriminative ability. Functional and clinical impairment persisted at six months, with significant dyspnoea, ongoing 6MWT limitation, and higher rehospitalisation rates in the PF group. These findings provide a comprehensive clinical and radiological characterisation of post-COVID PF from an Indian tertiary care perspective, support risk-stratified post-COVID pulmonary surveillance programmes targeting high-acuity COVID-19 survivors, and establish KL-6 and TGF-β1 as clinically actionable fibrotic biomarkers warranting incorporation into post-COVID follow-up protocols. Larger multi-centre Indian studies with extended longitudinal follow-up are needed to delineate the natural history and optimal management of post-COVID pulmonary fibrosis in this population.

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REFERENCES

1. Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JV. A clinical case definition of post-COVID-19 condition by a Delphi consensus. Lancet Infect Dis. 2022;22(4):e102–7.
2. Myall KJ, Mukherjee B, Castanheira AM, Lam JL, Benedetti G, Mak SM, Preston R, Thillai M, Dewar A, Molyneaux PL, West AG. Persistent post–COVID-19 interstitial lung disease. An observational study of corticosteroid treatment. Annals of the American Thoracic Society. 2021 May;18(5):799-806.
3. George PM, Wells AU, Jenkins RG. Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy. Lancet Respir Med. 2020;8(8):807–15.
4. Raman B, Cassar MP, Tunnicliffe EM, Filippini N, Griffanti L, Alfaro-Almagro F, Okell T, Sheerin F, Xie C, Mahmod M, Mózes FE. Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post-hospital discharge. EClinicalMedicine. 2021 Jan 1;31:100683.
5. Shah AS, Wong AW, Hague CJ, Murphy DT, Johnston JC, Ryerson CJ, Carlsten C. A prospective study of 12-week respiratory outcomes in COVID-19-related hospitalisations. Thorax. 2021 Apr 1;76(4):402-4.
6. American Thoracic Society. Committee on proficiency standards for clinical pulmonary function laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166(1):111-7.
7. Ohshimo S, Bonella F, Guzman J, Costabel U. Serum KL-6 in idiopathic pulmonary fibrosis: potential role in disease prediction and monitoring. Expert Rev Respir Med. 2022;16(1):5–10.
8. Rai DK, Sharma P, Kumar R. Post COVID 19 pulmonary fibrosis. Is it real threat? Indian J Tuberc. 2021;68(3):330–3.
9. Chopra V, Flanders SA, O'Malley M, Malani AN, Prescott HC. Sixty-day outcomes among patients hospitalized with COVID-19. Ann Intern Med. 2021;174(4):576–8.
10. Distler O, Highland KB, Gahlemann M, Azuma A, Fischer A, Mayes MD, Raghu G, Sauter W, Girard M, Alves M, Clerisme-Beaty E. Nintedanib for systemic sclerosis–associated interstitial lung disease. New England Journal of Medicine. 2019 Jun 27;380(26):2518-28.