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Post-COVID Interstitial Lung Disease: How do We Deal with This New Entity?

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Background: In the postacute phase of coronavirus disease-2019 (COVID-19), survivors may have persistent symptoms, lung function abnormalities, and sequelae lesions on thoracic computed tomography (CT). This new entity has been defined as post-COVID interstitial lung disease (ILD) or residual disease.

Aims: To evaluate the characteristics, risk factors and clinical significance of post-COVID ILD.

Study Design: Multicenter cross-sectional analysis of data from a randomized clinical study.

Methods: In this study, patients with persistent respiratory symptoms 3 months after recovery from COVID-19 were evaluated by two pulmonologists and a radiologist. post-COVID ILD was defined as the presence of respiratory symptoms, hypoxemia, restrictive defect on lung function tests, and interstitial changes on follow-up high-resolution computed tomography (HRCT).

Results: At the three-month follow-up, 375 patients with post-COVID-19 syndrome were evaluated, and 262 patients were found to have post-COVID ILD. The most prevalent complaints were dyspnea (n = 238, 90.8%), exercise intolerance (n = 166, 63.4%), fatigue (n = 142, 54.2%), and cough (n = 136, 52%). The mean Medical Research Council dyspnea score was 2.1 ± 0.9, oxygen saturation was 92.2 ± 5.9%, and 6-minute walking distance was 360 ± 140 meters. The mean diffusing capacity of the lung

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for carbon monoxide was 58 ± 21, and the forced vital capacity was 70% ± 19%. Ground glass opacities and fibrotic bands were the most common findings on thoracic HRCT. Fibrosis-like lesions such as interlobular septal thickening and traction bronchiectasis were observed in 38.3% and 27.9% of the patients, respectively. No honeycomb cysts were observed. Active smoking [odds ratio (OR), 1.96; 95% confidence interval (CI), 1.44-2.67), intensive care unit admission during the acute phase (OR, 1.46; 95% CI, 1.1-1.95), need for high-flow nasal oxygen (OR, 1.55; 95% CI, 1.42-1.9) or non-invasive ventilation (OR, 1.31; 95% CI, 0.8-2.07), and elevated serum lactate dehydrogenase levels (OR, 1.23; 95% CI 1.18-1.28) were associated with the development of post-COVID ILD. At the 6-month follow-up, the respiratory symptoms and pulmonary functions had improved spontaneously without any specific treatment in 35 patients (13.4%). The radiological interstitial lesions had spontaneously regressed in 54 patients (20.6%).

Conclusion: The co-existence of respiratory symptoms, radiological parenchymal lesions, and pulmonary functional abnormalities which suggest a restrictive ventilatory defect should be defined as post-COVID-19 ILD. However, the term "fibrosis" should be used carefully. Active smoking, severe COVID-19, and elevated lactate dehydrogenase level are the main risk factors of this condition. These post-COVID functional and radiological changes could disappear over time in 20% of the patients.

INTRODUCTION

Post-COVID syndrome, also known as long COVID, is a heterogeneous condition with various presentations of multisystem involvement, including persistent symptoms of coronavirus disease-2019 (COVID-19).[1] The most frequent complaints of this syndrome are pulmonary symptoms, including shortness of breath, cough, and chest pain.[2,3] In patients with severe COVID-19 pneumonia and acute respiratory distress syndrome (ARDS), dyspnea persists for 30-60 days after discharge.[4] Fatigue (87%), shortness of breath (71%), and chest discomfort (44%) are the most prevalent symptoms persisting three months after regardless of the disease severity.[5] Furthermore, dyspnea is present in half of the hospitalized patients with COVID-19 at the post-discharge three-month follow-up regardless of the need for intensive care unit (ICU) care.[6] Recent studies have demonstrated that breathlessness persists in 10-21% of the patients with COVID-19 even one year after discharge.[7,8]

The prevalence of lung parenchymal lesions on computed tomography (CT) at 3-4 months after a COVID-19 infection ranges from 42% to 89%.[9-11] In the study by Han et al.[12], this prevalence was 62% at six months. Furthermore, they demonstrated that 35% of the patients exhibited parenchymal bands, irregular opacities, traction bronchiectasis, and/or honeycombing, which were defined as fibrosis-like changes. In the study by Caruso et al.[13], the rate of fibrotic-like changes was 72%. However, the clinical importance of these radiological findings is controversial.[14,15] Zhao et al.[8] reported that 71.2% of the patients with COVID-19 exhibit CT changes, including ground glass opacities (GGOs), subpleural lines and nodules, even one year after recovery.[16,17] In addition, organizing pneumonia and pulmonary fibrosis have been reported in a small group.[18-20]

Pulmonary function abnormalities, especially restrictive ventilatory defect, in spirometry has been detected following a COVID-19 infection, with a moderate reduction in the lung diffusion capacity for carbon monoxide (DL_{CO}).[8,21] In an observational study of 113 COVID-19 survivors, exercise-induced hypoxemia, reduced 6 minute walking distance (6MWD), and lung diffusion deficit were reported at 4 months among patients with severe pulmonary involvement.[22] In another study, the DL_{CO} impairment persisted even one year after discharge in 10.6% of the patients with COVID-19.[8] Although most of the survivors of the Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome outbreaks made a full recovery without sequelae, a systematic meta-analysis revealed that the decrease in diffusion capacity is observed even 20 years after the infection.[23]

The aforementioned study results indicate that in the post-acute phase, COVID-19 survivors may have persistent respiratory symptoms, lung function abnormalities, and sequelae lesions on thoracic CT. Hence, should this new phenomenon be defined as post-COVID interstitial lung disease (ILD) or a residual disease? Considering the available data, post-COVID ILD can be defined as the presence of the following at the 3-month follow-up after recovery from COVID-19: 1) persistent COVID-19 respiratory symptoms; 2) hypoxemia at rest and/or during exercise; 3) restrictive ventilatory defect (forced vital capacity [FVC] of < 80% of the predicted normal and/or DL_{CO} of < 80% of the predicted normal); and 4) interstitial changes such as GGOs, subpleural and/or fibrotic bands, and consolidations as well as fibrotic-like changes on follow-up high-resolution computed tomography (HRCT)/CT of the thorax. The global burden of post-COVID ILD could be high considering the massive scale of the COVID-19 pandemic, even if it is prevalent in only a small number of patients. Moreover, progression to pulmonary fibrosis can be challenging in several aspects. The survival rate of patients with fibrosing lung disease is low,[24] and the risk of malignancy increases according to the amount of fibrotic tissue.[25] Therefore, it is crucial to determine the clinical importance of post-COVID-19 abnormalities. To achieve this, the clinical and radiological characteristics of post-COVID ILD must be described. Furthermore, the factors associated with acute COVID-19 infection should be evaluated to predict which patients are at risk for developing post-COVID ILD. Thus, in this study, we aimed to assess the characteristics, risk factors, and clinical significance of post-COVID ILD.

METHODS

Study Design

This cross-sectional analysis included patients from the STERCOV-ILD study (NCT: 04988282), a phase III, 12-week, multicenter, randomized, open label, controlled study in patients with post-COVID-19 syndrome and interstitial sequela lesions. The study

was approved by the Yüksek İhtisas University Institutional Ethics Committee (approval number: 2021-01; date: 31.03.2021), and it adhered to the ethical principles outlined in the Declaration of Helsinki.

Patient Characteristics

In this study, patients aged 18-80 years with long COVID-19 syndrome were examined ≥ 3 months after recovery from COVID-19. The following were the inclusion criteria of the STERCOV-ILD study: persistent post-COVID-19 respiratory symptoms; hypoxemia at rest and/or during exercise; restrictive ventilatory defect (FVC of < 80% of the predicted normal and/or DL_{CO} of < 80% of the predicted normal); and interstitial changes on the follow-up thoracic HRCT/CT. This criterion were also considered diagnostic criterion exclusion criteria: normal lung imaging test (chest X-ray or CT), pre-pandemic diffuse parenchymal lung disease, cystic bronchiectasis, decompensated heart failure, patients with contraindications for pulmonary function tests (PFT), patients who could not cooperate with the test or did not provide written consent, and pregnant or breastfeeding women. Absence of pre-existing ILD was confirmed via a pre-pandemic chest CT. Previous thoracic radiological studies of all the eligible patients were screened via the national electronic patient database. A total of 375 patients with suspected post-COVID ILD were referred by a pulmonologist. These patients were evaluated by a team of two pulmonologists and one radiologist. Finally, 262 patients were included in the study. Informed written consent was obtained from all the participants before being enrolled in the study.

Assessments and Outcomes

Persistent COVID-19 symptoms, modified Medical Research Council (m-MRC) dyspnea score, oxygen saturation (SpO_2) on room air, DL_{CO}, and thoracic CT/HRCT were assessed. Additionally, the 6 minutes walking test (6MWT), PFT, and blood tests, including complete blood count, liver and kidney function tests, and estimation of C-reactive protein, troponin I, D-dimer, fibrinogen, and ferritin levels, were performed. Thoracic HRCTs were examined for the presence of interstitial lesions suggestive of post-COVID ILD by a radiologist (NH) with experience in thoracic radiology from an academic tertiary-care center. The characteristics of 262 patients with post-COVID ILD were compared with the characteristics of 97 patients without post-COVID interstitial lung abnormalities. Furthermore, the risk factors for post-COVID pulmonary disease were evaluated. The patients with post-COVID ILD were followed-up and re-examined at 6 months.

Thoracic CT

Thoracic HRCTs were examined for the presence of interstitial lesions suggestive for post-COVID ILD. Furthermore, previous CTs were examined for suspicious findings suggestive of other ILD, including definite usual interstitial pneumonia pattern, cysts, nodules, predominance of honeycombing, mediastinal lymphadenopathies, and extraparenchymal findings (e.g., esophageal dilatation, pleural effusion, and pulmonary arterial enlargement). To exclude pre-existing or occult ILD, the previous thoracic images and medical records of the study patients in the national electronic patient database were screened. The radiologic patterns were categorized into the following three groups according to the predominance of the GGOs or bands: GGOs, fibrotic bands, and combined pattern. The extension of the radiological lesions was classified as follows: "extensive", involvement of > 25% of lung parenchyma and "mild", involvement of < 25% of lung parenchyma. The CT score was calculated according to the involvement of the lobes of the two lungs on a scale of 0-5, with zero indicating no involvement and five indicating > 75% involvement.[31] The CTs were also assessed for predominant pattern, septal thickening, and bronchiectasis. At the six-month follow-up, a CT was obtained in the patients with post-COVID ILD. The difference in the predominant pattern and involvement scores between the initial and follow-up CTs were assessed.

Statistical analysis

Conformity of the continuous variables to normal distribution was evaluated using the Kolmogorov-Smirnov test. Group effects were evaluated in two groups: the post-COVID ILD group and the control group. The Student's t-test was used to assess differences in continuous variables between the groups when the variables were normally distributed and homoscedastic. The Mann-Whitney U test was used to compare the variables if they were not normally distributed. The chi-squared and Fisher's exact tests were used to compare the categorical data between the groups. Normally distributed continuous variables are expressed as means and standard deviations, and non-normally distributed data are expressed as medians with interquartile ranges (interquartile range, 25%-75%). The categorical (nominal) variables are presented as numbers and percentages (%). Univariate logistic regression analyses were performed to identify potential risk factors of post-COVID ILD at twelve weeks. The results are expressed as odds ratios (ORs) and 95% confidence intervals (CIs). All variables were tested individually. Variables with a p value of < 0.05 in the univariate analysis were adjusted for treatment and baseline stratification and analyzed using multivariate logistic regression. A p value of < 0.05 was considered statistically significant for all analyses.

RESULTS

A total of 359 patients were included in the study (Figure 1). Of the 359 patients, 262 had post-COVID ILD. The mean age of the patients was 60 ± 12 years, and 45.7% of the patients were female (Table 1). The baseline sociodemographic and clinical characteristics, laboratory test findings, and lung function test results of the patients with and without post-COVID ILD are shown in Table 1. Differences in the severity of acute COVID-19 according to the treatment area and respiratory failure between the two study groups are shown in Figure 2.

In the post-COVID ILD group, the most prevalent persistent symptoms were dyspnea (n = 238, 90.8%), exercise intolerance (n = 166, 63.4%), fatigue (n = 142, 54.2%), and cough (n = 136, 52%) (Table 2). The most prevalent comorbidities in the group were hypertension (n = 128, 48.8%), diabetes (n = 88, 33.6%), heart diseases (n = 40, 15.3%), asthma (n = 20, 7.6%) and chronic obstructive pulmonary disease (n = 15, 5.7%). During the acute phase of COVID-19, 85

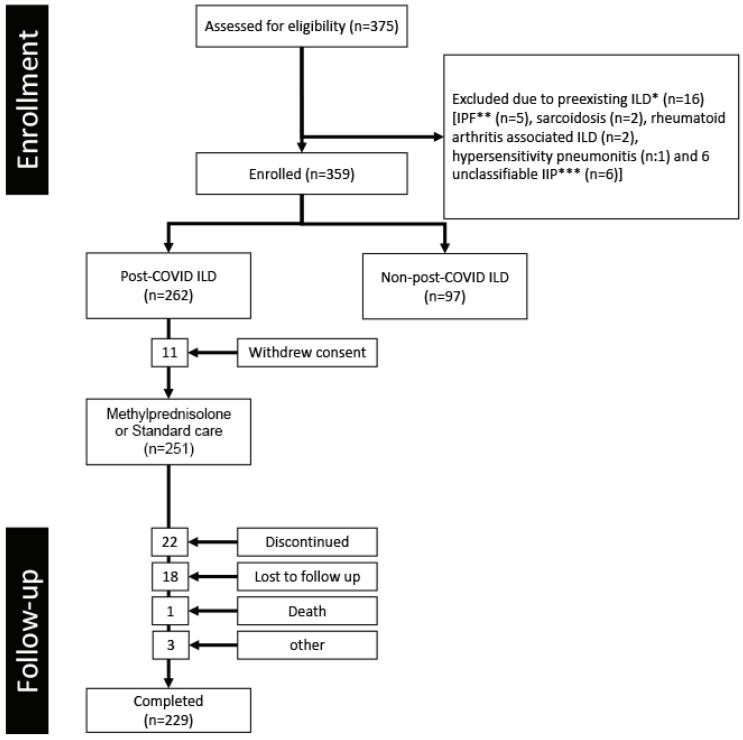

FIG. 1. Flow diagram of the study.

TABLE 1. Baseline Characteristics of the Study Patients.

Characteristics	Overall (n = 359)	Control group (n = 97)	Post-COVID ILD group (n = 262)	*p* value
Age, years	60 ± 12	60 ± 12	59 ± 11	0.216
Sex				
Male	195 (54.3%)	53 (54.7%)	142 (54.2%)	0.379
Female	164 (45.7%)	56 (57.8%)	108 (41.2%)	
Smoking status				
Never smoked	221 (61.6%)	65 (67%)	156 (59.5%)	
Active smoker	22 (6.1%)	2 (2%)	20 (7.6%)	0.049*
Ex-smoker	116 (32.3%)	30 (31%)	86 (32.8%)	
Body mass index, kg/m^2	30.5 ± 6.4	30.4 ± 4.8	30.6 ± 7.6	0.614
Comorbidities				
Hypertension	172 (47.9%)	44 (45.3%)	128 (48.8%)	0.163
Diabetes	121 (33.7%)	33 (34%)	88 (33.6%)	0.642
Heart disease	57 (15.9%)	17 (17.5%)	40 (15.3%)	0.553
Asthma	29 (8%)	9 (9.2%)	20 (7.6%)	0.765
COPD	21 (5.8%)	6 (6.1%)	15 (5.7%)	0.879
Cancer	12 (3.3%)	2 (2%)	10 (3.8%)	0.685
CTD	4 (1.1%)	1 (1%)	3 (1.1%)	NA
Corticosteroid use during the acute phase of COVID-19	272 (75.8%)	70 (72.2%)	202 (77%)	0.794
Anti-cytokine use during the acute phase of COVID-19	60 (16.7%)	10 (10.3%)	50 (19%)	0.019*

TABLE 1. Continued

Characteristics	Overall (n = 359)	Control group (n = 97)	Post-COVID ILD group (n = 262)	*p* value
Acute phase symptoms				
Dyspnea	299 (83.2%)	50 (51.5%)	249 (95%)	0.007*
Exertion intolerance	218 (60.7%)	41 (42.2%)	177 (67.6%)	0.047*
Fatigue	213 (59.3%)	60 (61.8%)	153 (58.3%)	0.379
Cough	210 (58.5%)	63 (65%)	147 (56.1%)	0.516
Myalgia	134 (37.3%)	38 (39.2%)	96 (36.6%)	0.427
Modified MRC score	1.8 ± 0.8	0.6 ± 0.3	2.1 ± 0.9	< 0.001*
Oxygen saturation, (%)	94.1 ± 3.4	96.1 ± 3.4	92.2 ± 5.9	< 0.001*
FEV_1, L	2.28 ± 0.75	2.36 ± 0.82	2.2 ± 0.66	0.106
FEV_1,%	79 ± 19	85 ± 19	75 ± 15	0.007*
FVC, L	2.59 ± 0.88	2.69 ± 0.97	2.42 ± 0.76	0.158
FVC, %	73 ± 15	81 ± 9	70 ± 19	0.012*
FEV_1/FVC%	87 ± 9	87 ± 8	87 ± 10	0.397
DL_{CO},%	64 ± 21	70 ± 20	58 ± 21	0.036*
6MWD, m	394 ± 146	428 ± 151	360 ± 140	0.015*
Inflammatory markers				
C-reactive protein, mg/l	12.8 (10.6-31.8)	7.5 (2.8-8.5)	20 (12.9-38.7)	0.89
D-dimer, mg/dl	616.4 (307-921)	260.6 (47-648)	1,574 (574-2,870)	0.018*
Lactate dehydrogenase, U/l	442 ± 65	235 ± 47	649 ± 75	0.022*
Ferritin, µg/l	411 ± 130	319 ± 107	448 ± 146	0.046*
Fibrinogen, mg/dl	363 ± 66	372 ± 60	356 ± 70	0.61

Data are presented as mean ± standard deviation or n (%) except for C-reactive protein and D-dimer levels which are presented as medians (interquartile ranges 25%-75%). *Results are significantly different between the groups ($p < 0.05$). COVID, coronavirus; ILD, interstitial lung disease; COPD, chronic obstructive pulmonary disease; CTD, connective tissue disease; DL_{CO}, diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume at one second; FVC, forced vital capacity; HFNC, high-flow nasal canula; ICU, intensive care unit; MRC, Medical Research Council; MV, mechanical ventilation; 6MWD, 6-minute walking distance.

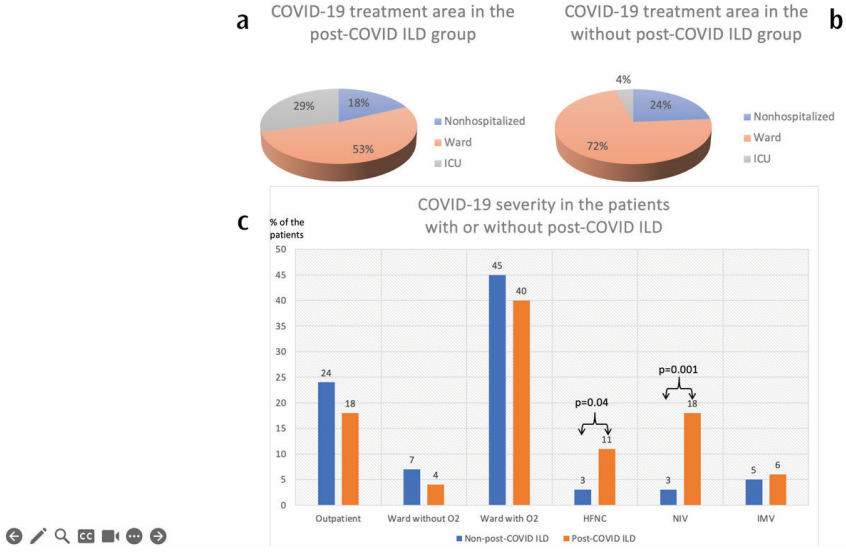

FIG. 2. Comparison of the severity of the acute phase of COVID-19 between the post-COVID ILD group and the control group. Upper panel: Distribution of the patients in each group [(a) patients with post-COVID ILD and (b), controls] according to the treatment area. Lower panel (c): Distribution of the patients according to the method of respiratory failure treatment in the study groups.
COVID-19, coronavirus disease-2019; ILD, interstitial lung disease; ICU, intensive care unit; HDNC, high-flow nasal canula; NIV, non-invasive ventilation.

patients (32.4%) required ICU admission, 137 patients (52.3%) were treated in the ward, and 40 patients (15.3%) did not require hospitalization. COVID-19 severity was classified according to the method of respiratory failure treatment as follows: conventional oxygen (n = 105, 40%), high-flow nasal oxygen (n = 29, 11%), non-invasive ventilation [(NIV); n = 46, 17.6%], and intubation (n = 15, 5.7%) (Figure 2). During the acute phase of COVID-19, 202 patients (77%) were administered systemic corticosteroids, and 50 patients (19%) were administered anti-cytokines. The mean m-MRC dyspnea score was 2.1 ± 0.9, and mean SpO_2 on room air was 92.2 ± 5.9%. Ninety patients (34.4%) exhibited respiratory failure, and the mean 6MWD was 360 ± 140 meters. The PFT results are provided in Table 2. The mean DL_{CO} was 58 ± 21, and the mean FVC% was 70 ± 19%.

The radiological features of the study patients are included in Table 3. Thoracic HRCTs of the study patients revealed GGOs, fibrotic bands, and a mixed pattern in 35.3%, 33.3%, and 31.3% of the patients, respectively. Examples of interstitial lesions on the thoracic HRCT of five patients are shown in Figure 3. The radiological lesions involved > 25% of the lung parenchyma in 64.5% of the patients. Approximately 47.3% of the participants exhibited peripheral parenchymal infiltrates, while 52.7% of the participants exhibited both peripheral and central lesions. The mean CT severity score was 13.5 ± 5. Approximately 38.3%, 28%, and 17.4% of the patients exhibited interlobular septal thickening, central traction bronchiectasis, and peripheral cylindrical bronchiectasis, respectively.

TABLE 2. Clinical Characteristics and Pulmonary Function Test Results of Patients with Post-COVID ILD.

Characteristics	Data
Persistent symptoms, n (%)	
Dyspnea	238 (90.8%)
Exertion intolerance	166 (63.4%)
Fatigue	142 (54.2%)
Cough	136 (52%)
Myalgia	85 (32.4%)
Modified MRC score, mean ± SD	2.1 ± 0.9
Oxygen saturation at ambient air, mean ± SD	92.2 ± 5.9
Patients with respiratory failure, n (%)	90 (34.4%)
6-minute walking distance, mean ± SD	360 ± 140
FEV_1 (L), mean ± SD	2.2 ± 0.66
FEV_1%, mean ± SD	75 ± 15
FVC (L), mean ± SD	2.42 ± 0.76
FVC%, mean ± SD	70 ± 19
FEV_1/FVC%, mean ± SD	87 ± 10
DL_{CO}%, mean ± SD	58 ± 21
DLCO/VA (%), mean ± SD	89.6 ± 27.2

Data are as means and standard deviations (SDs) or n (%). COVID, coronavirus; ILD, interstitial lung disease; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; FEV_1, forced expiratory volume at one second; FVC, forced vital capacity; MRC, Medical Research Council.

Several factors were significantly associated with post-COVID ILD at the 3-month follow-up. These factors included active smoking (OR, 3.37; 95% CI, 1.8-6.28), ICU admission during the acute phase (OR, 4.55; 95% CI, 1.72-8.69), need for high-flow nasal oxygen (OR, 4.53; 95% CI, 2.58-7.9), need for NIV (OR, 4.1; 95% CI, 2.5-6.5), and anti-cytokine use during the acute phase (OR, 1.72; 95% CI, 1.2-2.42). Among the acute symptoms, dyspnea at rest (OR, 1.86; 95% CI 1.33-2.6) and exercise intolerance (OR, 1.69; 95% CI, 1.18-2.38) were strongly associated with post-COVID ILD. Furthermore, elevated lactate dehydrogenase (OR, 1.32; 95% CI, 1.12-1.38), D-dimer (OR, 1.24; 95% CI, 0.96-1.62), and ferritin (OR, 1.18; 95% CI, 0.86-1.63) levels were significantly associated with post-COVID interstitial abnormalities (Table 4). Multivariate regression analysis revealed that the following variables were associated with post-COVID-19 ILD at the 3-month follow-up: active smoking (OR, 1.96; 95% CI, 1.44-2.67), ICU admission during the acute phase (OR, 1.46; 95% CI, 1.1-1.95), high-flow nasal oxygen (OR, 1.55; 95% CI, 1.42-1.9), need for NIV (OR, 1.31; 95% CI, 0.8-2.07), and elevated serum lactate dehydrogenase level (OR, 1.23; 95% CI, 1.18-1.28) (Table 4).

Of the 262 patients in the post-COVID ILD group, 229 were assessed at 6 months after recovery. At the 6-month follow-up, 35 patients (13.4%) reported no respiratory complaints, and the pulmonary function improved without any specific treatment.

TABLE 3. Radiological Features of the Patients with Post-COVID ILD.

Thoracic CT findings	Results
Radiological pattern	
- Ground glass opacities	92 (35.3%)
- Fibrotic bands	88 (33.3%)
- Mixed pattern	82 (31.3)
Distribution of the lesions	
- Peripheral	124 (47.3%)
- Peripheral + central	138 (52.7%)
Extension of the lesions	
- Mild (< 25 %)	93 (35.5%)
- Diffuse (> 25 %)	169 (64.5%)
CT score (mean ± SD)	13.5 ± 5
CT score	
- < 15	132 (50.4%)
- > 15	130 (49.6%)
Density of ground glass opacities	
- Mild	102 (38.8%)
- Dense	160 (61.2%)
Septal thickening	101 (38.3%)
Central traction bronchiectasis	73 (27.9%)
Peripheral cylindrical bronchiectasis	46 (17.4%)

Data are presented as mean ± SD or n (%). COVID, coronavirus; ILD, interstitial lung disease; CT, computed tomography; SD, standard deviation.

An improvement in the radiological interstitial lesions without treatment was observed in 54 patients (20.6%). A comparison of the functional status trajectory over time between patients with radiological improvement despite the absence of a specific treatment (n = 54) and patients without radiological resolution (n = 51) is given in Figure 4.

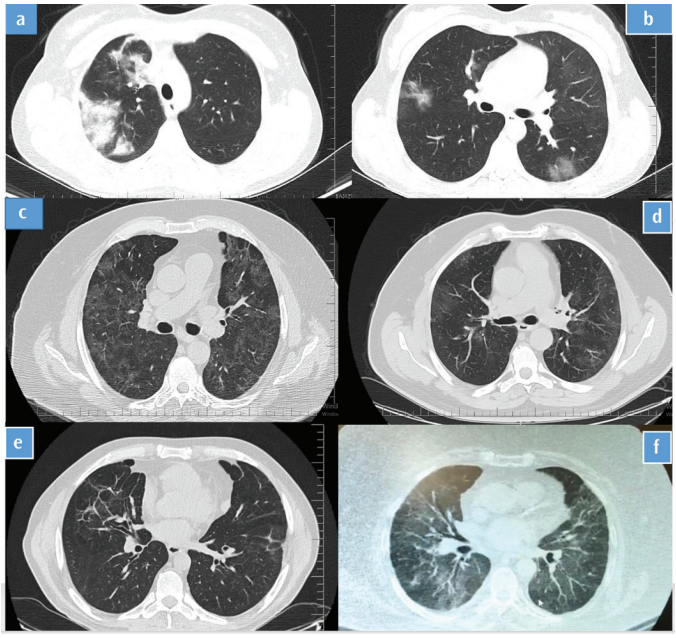

FIG. 3. HRCT images of five patients with post-COVID ILD. (a) Peripheral and centric consolidations in the RUL and (b) peripheral GGOs in the LLB in one patient. (c) Diffuse GGOs in another patient. (d) Peripheral, multifocal, patchy GGOs. (e) Parenchymal lesions in the RUL and subpleural fibrotic bands in the LLB. (f) Extensive GGOs and traction bronchiectasis.
HRCT, high-resolution computed tomography; COVID, coronavirus; ILD, interstitial lung disease; RUL, right upper lobe; GGO, ground glass opacity; LLB, left lower lobe.

DISCUSSION

This study's findings revealed the co-existence of pulmonary functional defects and lung parenchymal lesions on radiological studies in patients with persistent respiratory symptoms at 3 months after a COVID-19 infection. Up to 70% of patients with post-COVID pulmonary findings at the 3-month follow-up, exhibited symptoms at the 6-month follow-up. However, our results demonstrated that spontaneous clinical and functional recovery is possible in patients with post-COVID syndrome. Furthermore, regression of the radiologically visible interstitial lesions was observed in 20% of the patients. Although some patients improve over time, this entity can cause severe complications such as pulmonary fibrosis, chronic respiratory failure, and lung malignancy. In this study, fibrotic-like lesions such as septal thickening and traction bronchiectasis were observed in approximately 38% of the patients. No honeycomb cysts were observed in our study.

Lung parenchymal infiltrations on thoracic HRCTs of patients with COVID-19 pneumonia could persist for a long time, and the regression of radiological abnormalities may alter. Interstitial lung lesions following COVID-19 may differ in pattern and severity. Furthermore, long-term radiological features are not uniform.[6-9,12,13,15-17] Persistent radiological abnormalities may vary from GGOs to organizing pneumonia and even fibrotic-like lesions.[6-9,12,13,15-17] Frequently reported patterns are GGOs, reticulations, and consolidations,[6,26-29] which are seldom linked to fibrosis and tend to disappear over time.[3,26,30,31] In this study, we identified three patterns of interstitial lesions: GGOs, fibrotic bands, and mixed pattern. Our radiological findings are consistent with those of previous studies in which GGOs were reported as the most common pattern in post-COVID ILD. Furthermore, we observed fibrotic bands that were thicker than reticulations. At the 6-month follow-up, the rate of fibrosis-like changes, including parenchymal bands, irregular reticular opacities, traction bronchiectasis, and/or honeycombing, is reportedly 35%.[12] In the study by Caruso et al.[13], this rate was 72%. However, some authors with expertise in ILDs

TABLE 4. Risk Factors for the Development of Post-COVID ILD.

	Univariate OR (95% CI)	p	R^2	Multivariate OR (95% CI)	p
Smoking	3.37 (1.8-6.28)	< 0.001	0.017	1.96 (1.44-2.67)	0.001
ICU admission during the acute phase	4.55 (1.72-8.69)	< 0.001	0.039	1.46 (1.1-1.95)	0.001
Need for HFNC during the acute phase	4.53 (2.58-7.9)	< 0.001	0.033	1.55 (1.42-1.9)	0.005
Need for NIV during the acute phase	4.1 (2.5-6.5)	< 0.001	0.038	1.31 (0.8-2.07)	0.013
Anti-cytokine administration during the acute phase	1.72 (1.2-2.42)	0.003	0.011	1.05 (1.004-1.1)	0.055
Dyspnea during the acute phase	1.86 (1.33-2.6)	< 0.001	0.014	1.47 (1.36-2.22)	0.926
Exercise intolerance during the acute phase	1.69 (1.18-2.38)	0.003	0.011	0.997 (0.994-1)	0.29
D-dimer level	1.24 (0.96-1.62)	0.04	0.003	0.98 (0.86-1.11)	0.737
Lactate dehydrogenase level	1.32 (1.12-1.38)	< 0.001	0.176	1.23 (1.18-1.28)	< 0.001
Ferritin level	1.18 (0.86-1.63)	0.031	0.001	0.98 (0.86-1.13)	0.832

COVID, coronavirus; ILD, interstitial lung disease; OR, odds ratio; CI, confidence interval; HFNC, high-flow nasal canula; ICU, intensive care unit; NIV, non-invasive mechanical ventilation.

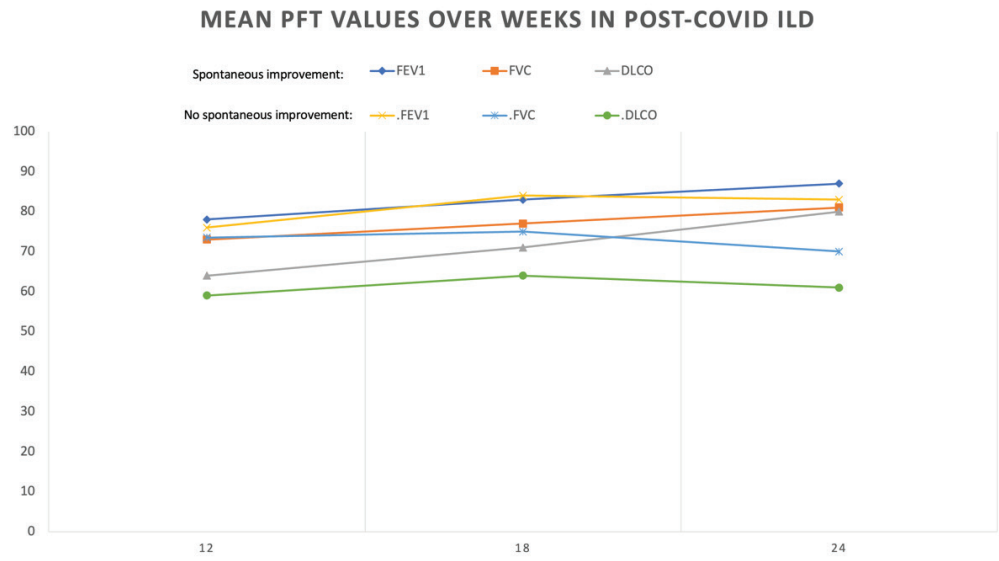

FIG. 4. Course of the pulmonary function tests over 6 months of the 105 patients with post-COVID ILD who did not receive any treatment. The dark blue, orange, and gray lines depict the course of FEV_1, FVC, and DL_{CO} in 54 patients with spontaneous radiological improvement. The yellow, light blue, and green lines depict the course of FEV_1, FVC, and DL_{CO} in 51 patients without spontaneous radiological improvement.
FEV1, forced expiratory volume at one second; FVC, forced vital capacity; DLCO, diffusing capacity of the lung for carbon monoxide.

and thoracic radiology have stated that most of these radiological findings do not have any clinical importance.[14,15] In our study, the proportion of patients with interlobular septal thickening was similar to that in the study by Han et al.[12] However, the proportion of other fibrotic changes such as traction bronchiectasis in our study was lower than that in previous studies. Thus, although clinicians should be aware of the risk of lung fibrosis, the presence of fibrosis-like changes is not indicative of progressive pulmonary fibrosis in each patient. Based on our data and that of previous studies, COVID-19 survivors may develop post-COVID interstitial lesions that are characterized by GGO predominance and parenchymal and/or subpleural bands.[16,17]

Post-COVID radiological abnormalities are more frequently observed in patients with severe COVID-19 than in those with mild-to-moderate COVID-19, and the abnormalities are linked to the use of invasive mechanical ventilation.[6,27] Our findings are partially consistent with these findings. We found that ICU admission during the acute phase was a risk factor for post-COVID ILD. This may be attributable to the fact that ARDS and ventilator-induced lung injury could contribute to the radiological sequelae such as diffuse alveolar damage and fibrosis-like changes in patients admitted to the ICU. Nevertheless, regardless of the severity of the acute phase of COVID-19, post-COVID ILD can develop in patients who required ICU admission and/or mechanical ventilation as well as patients who were not hospitalized.

In one study, several patients with lung parenchymal lesions on thoracic CT did not have any pulmonary complaints, spirometry deficiency, or reduced 6MWT.[26] Only thoracic CT, rather than functional measurements, has been used to assess post-COVID ILD. Our study results demonstrate that both radiologically visible parenchymal lesions and lung function deficits co-exist in patients with persistent respiratory symptoms especially breathlessness and cough. Furthermore, the pulmonary function improved in addition to the resolution of radiological lesions in a group of patients who did not receive any treatment. However, the pulmonary function did not improve in patients with no radiological improvement. These results support the hypothesis that post-COVID ILD is a multi-faceted entity that consists of clinical, radiological, and functional elements. Thus, its diagnosis should not be solely based on radiological lesions. Therefore, the presence of all four inclusion criteria of the STERCOV-ILD study should be confirmed before diagnosing a patient with post-COVID ILD. This will help clinicians determine which patients with long COVID-19 require further evaluation, reducing the cost and risk of over-treatment. Before the final diagnosis of post-COVID ILD, pre-existing ILD must be ruled out by examining pre-pandemic radiological studies. Patients with previously suspected and/or diagnosed ILD and patients with suspicious radiological lesions indicative of ILD should be carefully evaluated.

Impaired PFTs are associated with respiratory symptoms and interstitial lung lesions, and they are reportedly more well-defined and consistent than radiological findings. Restrictive ventilatory dysfunction and reduced diffusion capacity are the main functional abnormalities in patients with post-COVID ILD.[2,6,22,26,30] The result of pulmonary function impairment in our study is similar to that of previous studies. The most common finding in post-COVID ILD is a mild-to-moderate decrease in FVC and DL_{CO}. In the present study, restrictive pulmonary dysfunction and a decrease in the diffusion capacity, FVC, SpO_2, and 6MWD were observed in the post-COVID ILD group. These values were significantly different from the values in the control group, in which the functional parameters were

within the normal ranges. Hence, we hypothesized that if lung parenchymal lesions exist even after recovery from COVID-19, the lung functions will be deficient, or vice versa. Furthermore, we believe that the co-existence of respiratory symptoms, functional defects, and radiological parenchymal lesions should be defined as a new entity, post-COVID ILD. Spontaneous recovery of post-COVID ILD is possible, and these patients must be closely monitored during follow-up visits.

The predisposing factors of post-COVID ILD remain unknown. In this study, we identified that active smoking status and ICU admission during the acute phase were important risk factors for the development of post-COVID ILD. This finding is similar to that of a meta-analysis on patient with long COVID-19 regardless of the presence of ILD.[32] The need for high-flow nasal oxygen or NIV during the acute phase of the disease and elevated serum lactate dehydrogenase levels were also associated with a high risk of developing post-COVID ILD. However, unlike other studies, female sex, obesity, and older age were not identified as risk factors for post-COVID ILD.[2,32] The need for ventilatory support and a more severe COVID-19 disease have also been reported as risk factors for post-COVID ILD.[2,6] The ICU admission and high-flow nasal oxygen or NIV may be associated with barotrauma, which is harmful to the lung tissue. The lung tissue damage may also be related to the more severe form of COVID-19 that requires ventilatory support. The elevated serum lactate dehydrogenase level in patients with post-COVID ILD may be attributed to systemic hyperinflammation. The key factors that mediate ILD in response to Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) are currently unknown and are hypothesized to be linked to the innate immune response, hyperactivation of immune cells, in particular macrophages, and high levels of proinflammatory and profibrotic cytokines.[33] Lung hyperinflammation and fibrosis due to the SARS-CoV-2 infection begins with the accumulation of immune cells in the lung micro-environment and macrophage activation, which leads to dysregulation of tissue repair.[34-37] Hyperinflammation, lysis of immune cells, and lactate dehydrogenase release from these lytic cells might increase the serum lactate dehydrogenase levels.

Implementing detailed clinical examinations for long COVID into routine clinical practice involves several critical steps to ensure early detection, intervention, and comprehensive care of patients with post-COVID ILD. This process should begin with screening protocols to identify symptoms indicative of post-COVID ILD such as persistent shortness of breath, cough, exertion intolerance, and fatigue. Utilizing high-resolution imaging techniques, such as HRCT, in addition to PFT, will provide a detailed assessment of lung function abnormalities and radiological parenchymal lesions. Pulmonary function evaluation must include spirometry, carbon monoxide diffusion capacity, and exercise tests such as 6MWT. A holistic approach should be adopted for the evaluation and management of post-COVID ILD. The patients should be followed-up to ensure spontaneous improvement or facilitate timely adjustments for a treatment. Future studies that incorporate management and treatment protocols to better understand post-COVID ILD are required. The results of these studies will ensure the establishment of a standardized clinical guideline and or an approach to optimize patient outcomes.

A strength of our study is the exclusion of patients with pre-existing ILD. The ability to assess functional status via various tests such as spirometry, CO diffusion capacity, and 6MWT was another strength of the study. The limitations of this study were its short duration and relatively small sample size. Studies with larger sample sizes and longer follow-up are required to validate the persistence of COVID-19-related functional or radiological abnormalities over time.

In conclusion, the presence of persistent clinical symptoms, functional abnormalities, and radiological parenchymal lesions should be defined as a new entity, post-COVID ILD. However, the term “fibrosis” should be used carefully. Before making a diagnosis of post-COVID ILD, pre-existing occult ILD must be ruled out via a rigorous examination of pre-pandemic radiological images. Although some patients recover over time, most patients have persistent symptoms at the 6-month follow-up. Active smoking, ICU admission, need for high-flow nasal oxygen and/or NIV, and elevated lactate dehydrogenase levels are risk factors for post-COVID ILD. The condition developed in patients with mild disease as well as those with severe disease. Therefore, it cannot be only attributed to lung damage caused by ARDS and/or mechanical ventilation.

Ethics Committee Approval: The study was approved by the Yüksek İhtisas University Institutional Ethics Committee (approval number: 2021-01; date: 31.03.2021), and it adhered to the ethical principles outlined in the Declaration of Helsinki.

Informed Consent: Informed written consent was obtained from all the participants before being enrolled in the study.

Data Sharing Statement: The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

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