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Risk factors for the development of interstitial lung disease following severe COVID-19 pneumonia and outcomes of systemic corticosteroid therapy: 3-month follow-up

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Abstract. *Background:* We aimed to evaluate the pulmonary involvement status, its related factors, and pulmonary function test (PFT) results in the first month follow up in patients who were discharged for severe Covid-19 pneumonia; and to assess the efficacy of corticosteroid treatment on these parameters in severe pulmonary involvement patients. *Methods:* We retrospectively analyzed all consecutive patients who applied to our COVID-19 follow-up clinic at the end of the first month of hospital-discharge. Functional and radiological differences were compared after 3 months of corticosteroid treatment in severe pulmonary involvement group. *Results:* We analyzed 391 patients with "pulmonary parenchymal involvement" (PPIG) and 162 patients with "normal lung radiology" (NLRG). 122 patients in the PPIG (corticosteroid-required interstitial lung disease group (CRILD)) had severe pulmonary involvement with frequent symptoms and required corticosteroid prescription. Pulmonary involvement was more common in males and elder patients (P<0.001, for both). Being smoker and elderly were associated with a higher risk-ratio in predicting to be in PPIG (OR:2.250 and OR:1.057, respectively). Smokers, male and elderly patients, and HFNO2 support during hospitalization were risk factors for being a patient with CRILD (OR:2.737, OR:4.937, OR:4.756, and OR:2.872, respectively). After a three-months of methylprednisolone medication, a good response was achieved on radiological findings and PFT results in CRILD. *Conclusions:* In conclusion, after severe COVID-19 pneumonia, persistent clinical symptoms and pulmonary parenchymal involvement would be inevitable in elder and smoker patients. Moreover, corticosteroid treatment in patients with severe parenchymal involvement was found to be effective in the improvement of radiological and functional parameters.

Key words: COVID-19, interstitial involvement, steroid treatment, severe pneumonia

Introduction

Although some mutations in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 virus), Corona virus disease (COVID-19) still has enormous impact on public health, with increasing

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mortality and morbidities. Worldwide total number of confirmed cases exceeded 754 million and total death numbers reached 6.8 million to date (1). Beyond the mortality, post-COVID pulmonary sequelae and prolonged symptoms, for instance breathlessness, coughing, fatigue, renal failure, cardiac arrhythmias, neuropsychiatric symptoms including brain fog, dizziness, anxiety and depression, sleep disturbance are frequently reported in post-COVID survivors (2-5).

Current literature suggests that about 50% of COVID-19 survivors experiencing a long-term dyspnea, cough and other pulmonary symptoms. The etiologies of these persistent respiratory symptoms are not fully elucidated. Post-mortem studies on COVID-19 patients have demonstrated that during the disease, systemic inflammatory process brings about diffuse alveolar damage, exudation, and parenchymal alterations, resulting in pulmonary fibrosis (6-8). In some patients who survive following the severe COVID-19 disease, an ongoing systemic inflammatory process proceeds and causes interstitial pulmonary disease and fibrosis. In a study conducted in France, 42% of patients were complaining about breathlessness at the end of the 3rd month of discharge (9). Elderlies, male gender, smoking habit, comorbid diseases (such as diabetes mellitus), the requirement of mechanical ventilation during hospitalization, having severe acute respiratory distress syndrome (ARDS), the protracted elevation of inflammatory mediators (such as C-reactive protein (CRP), ferritin and Interleukin 6 (IL-6)) and elevated D-Dimer were reported as the most important risk factors for developing long term pulmonary involvement (10). There are also some other proposed factors or mechanisms for post-COVID-19 pulmonary involvement including prolonged symptoms of acute disease, immunomodulatory medications, organizing pneumonia, and secondary infections (11,12).

Thin section computed tomography (CT) of thorax plays a key role in the diagnosis of pulmonary involvement and also follow up of the patient after discharge (11). Especially, persistent pulmonary symptoms over one month after COVID-19 should be the clue for the suspicion of post-COVID pulmonary involvement. Although a certain period of time passes after the disease, these radiological abnormalities persist to some extent. In a study conducted by Wu et al., it was found that at the end of the first year of COVID-19, approximately 24% of the patients still had persistent radiological findings (13). In case of radiologically evident post-COVID lung involvement (organizing pneumonia, interstitial lung disease, etc.) in symptomatic patients, it is crucial to treat to protect against further morbidities.

In this study, we aimed to evaluate the pulmonary involvement status and pulmonary functions in survivors of hospitalized severe pneumonia and critically ill (followed in intensive care unit (ICU)) COVID-19 patients at the end of the 1st month of their discharge, and we sought to assess the efficacy of corticosteroids after 3 months of medication in severely affected patients.

Methods

This study was conducted between 1 September 2020 and 1 March 2021 as a single-center retrospective cohort study in the Department of Pulmonary Diseases, in Ankara City Hospital. Our hospital is a major tertiary care, training and research hospital in the capital city of Turkey. During the pandemic, evaluation of disease severity status, hospitalization, treatment and discharge decisions of the COVID-19 patients diagnosed by positive SARSCoV-2 polymerase chain reaction (PCR) test with compatible radiological findings in chest X-ray or thorax computed tomography (CT) scan were applied with accordance to the national guidelines for adult patients proposed by COVID-19 Scientific Board and Turkish Ministry of Health General Directorate of Public Health (14). According to this guideline, severe pneumonia cases defined as; "patients with symptoms of fever, muscle/joint pains, cough and sore throat, with tachypnea (≥30/minute) and SaO_2 level below ≤90% in room air, and bilateral diffuse pneumonia findings on chest X-ray or tomography" and critically ill (need to follow in ICU) patients defined as; "1- Respiratory rate ≥ 30/min, 2- PaO_2/FiO_2 <300, 3-Increased oxygen requirement during monitoring (Despite 5 L/min oxygen therapy, SaO2 <90% or PaO2 <70 mmHg), 4- Hypotension (systolic blood pressure (SBP) <90 mmHg and usual decrease of SBP more than 40 mmHg and mean arterial pressure <65 mmHg with tachycardia >100 beat/min), 5- Immunosuppression and development of acute organ dysfunction as acute kidney injury, acute disorder in liver function tests, confusion and acute bleeding diathesis, 6-Elevation of Troponin level and

arrhythmia, 7- Lactate >2 mmol, and 8- Capillary return and skin disorders such as cutis marmaratus".

Inclusion and exclusion criteria

In this study we included consecutive participants fulfilling criteria as follows; 1- Hospitalized as severe pneumonia and/or critically ill patients with age 18 and older, 2- Patients whose hospitalization records are fully accessible for "bed-side and ICU data, types of oxygen treatment modalities (nasal or mask oxygen, high flow nasal oxygen ($HFNO_2$)), noninvasive or invasive mechanical ventilation, prescribed medical treatments during hospitalization, laboratory and radiological findings, past medical history (comorbid diseases, smoking status), 3- At the 1st month of discharge; information about ongoing respiratory symptoms, pulmonary function test (PFT) (spirometry and diffusing capacity of the lung for carbon monoxide (DLCO) test), 6-minute walking test (6MWT) and radiological findings, 4- at the end of 3rd month of corticosteroid treatment; information about respiratory symptoms, PFT (spirometry and DLCO), 6MWT) and radiological findings.

During follow-up of post-COVID-19 patients, CT of the thorax was performed for the patients when an abnormal chest-X ray finding, or unexplainable symptom or physical examination finding was observed in the out-patient clinic as suggested in the British Thoracic Society Guideline (15).

We excluded patients under the age of 18, and patients with missing data (mentioned in inclusion criteria) in hospital recording system.

Review and scoring of thorax tomography

All CT of thorax of patients were reviewed and scored by two experienced radiologists, and any confusing or discordant results were unraveled by consensus and disputation. All CT findings were reviewed for the following aspects: laterality of involvement (right/left/bilateral), lobar involvement, central/peripheral/diffuse distribution, presence of radiological findings related to interstitial involvement (ground glass opacities, consolidation, crazy paving, parenchymal band atelectasis, reticular pattern, traction bronchiectasis, pneumothorax, pleural effusion, and honeycombing). CT findings were scored for the degree of interstitial involvement depends on dividing the lung into 5 lobes. Additionally, lobar involvement for each lobe was visually scored with a Likert scale between 0 and 5 ("0" representing healthy lung with no involvement, "1" representing less than 5%, "2" representing 5–25%, "3" representing 26–49%, "4" representing 50–74%, and "5" representing ≥75% involvement). The total score was calculated with the division of the sum of all lobar involvement to 5 (16,17). Moreover, initial (1st outpatient control) and follow-up (3rd month of treatment) features of tomography scan were compared for the regression.

We divided and compared groups as follows; 1- Patients with normal lung radiology group (NLRG) (scored "0"), 2- Patients with pulmonary parenchymal involvement group (PPIG) (scored "1" to "5"), and 3- patients who required corticosteroid treatment (evaluated by clinical and radiological findings to prescribe methylprednisolone, starting with 40 mg/day and dose tapered according to need of patient) defined as corticosteroid required interstitial lung disease group (CRILD). We also compared the efficacy of corticosteroid treatment on radiological findings, PFT, DLCO, and 6MWT at the end of 3rd month of methylprednisolone in CRILD.

This study was approved by the Clinical Investigations Ethical Committee of Yildirim Beyazit University with the number of 57/26.05.2021.

Statistical analysis

Statistical analyses of the study were performed using the Statistical Package for the Social Sciences for Windows v20.0 (SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test was performed to evaluate distribution status. Continuous variables were expressed as mean ± standard deviation [SD] or median (min.-max.) according to distribution status. Categorical variables were expressed as numbers and percentage. Proportions in different groups were compared using the Chi-square (χ^2) test. Student t-test (for means) or Mann–Whitney U-test (for medians) was used to compare the two independent groups according to distribution. For the multivariate analysis, firstly, possible factors were determined with univariate analyses. Data obtained from this analysis further entered into a logistics regression analysis to identify independent risk factors and detect confounding factors for the outcome of the severity of the radiological involvement and determine the requirement for the corticosteroid treatment.

The model fit assessment was tested by Hosmer-Lemeshow goodness of fit statistics. Power analyses were performed by G*Power 3.1 power analysis program. We obtained a 98% power by assuming a chi-square test with at least 232 patients (α error probability of 0.05 (sensitivity of 95%) and effect size of 0.30 (18). P values less than 0.05 were considered as statistically significant.

Results

A total of 972 patients admitted to post-COVID-19 outpatient clinic of our department were screened. After evaluation of these population according to study protocol, 419 patients were excluded. A total of 553 cases whose data were compatible to this study protocol were included to this study (Figure 1). Of these 553 patients, 391 (70.7%) patients (PPIG) had pulmonary involvement to some extent, and rest was evaluated as normal radiology.

The mean age of PPIG was 63.03±9.21 years and NLRG was 55.73±11.94 years (P <0.001). The proportion of male subjects was higher in PPIG than in NLRG (259 (66.2%) and 70 (43.2%), respectively) (P <0.001). The rate of smoker patients (actively smokers and ex-smokers) was higher in PPIG (49.3%) than in NLRG (22.3%) (P <0.001). 274 patients (70.1%) in PPIG and 36 (32.3%) patients

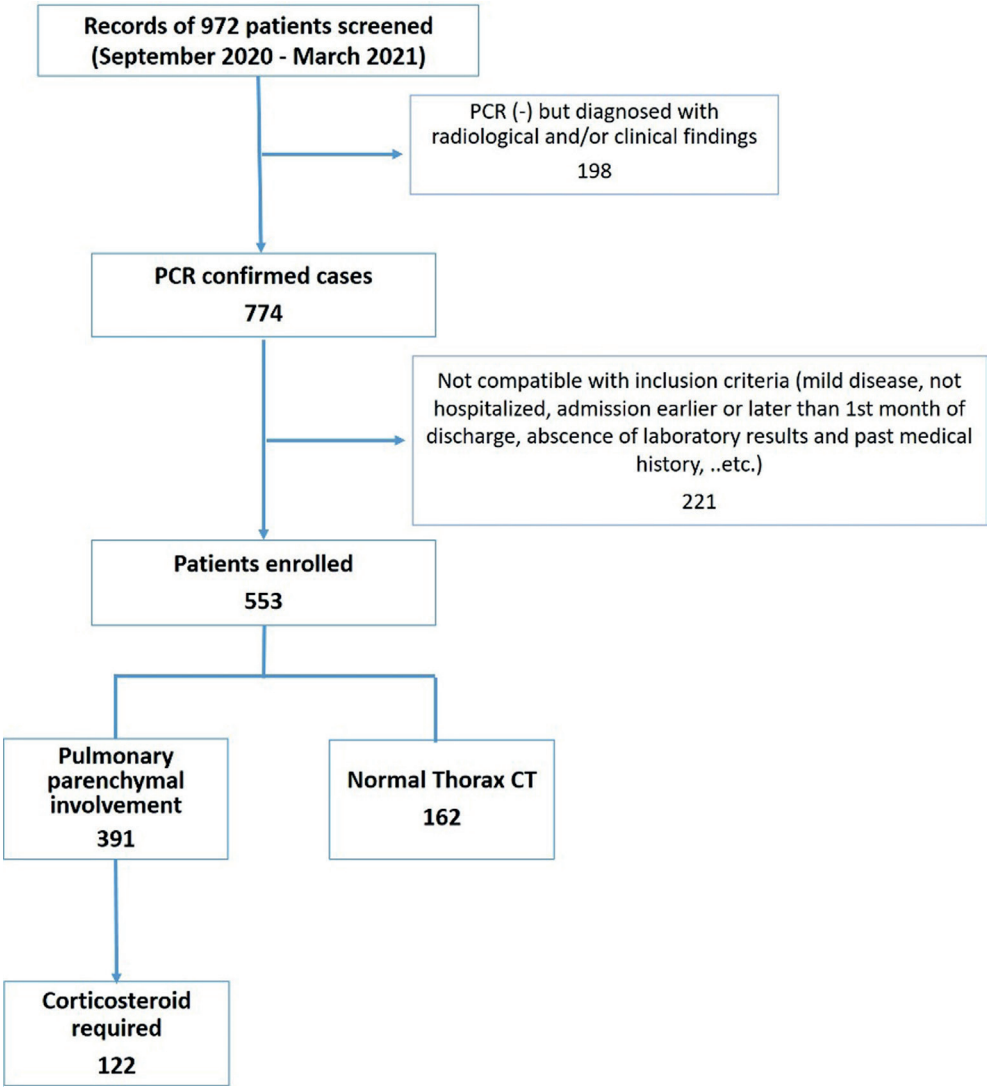

Figure 1. Flowchart of our study population (PCR: polymerase chain reaction, CT: Computed tomography).

in NLRG were smokers (current smokers or ex-smokers) (P <0.001). Smoking consumption (pack-year) status was similar in both groups. Having a comorbid disease was more frequent in the PPIG than in NLRG (274 (70.1%) and 97 (59.9%), respectively) (*P* =0.020). Chronic obstructive pulmonary disease (COPD) was more frequently seen in PPIG than in NLRG (*P*=0.012). During the period they were followed in the hospital, 143 patients (36.6%) in PPIG and 30 patients (18.5%) in NLRG were followed in the intensive care units (ICUs), others were followed only in the wards (*P*<0.001). Both hospital length of stay and ICU length of stay were longer in PPIG (*P*<0.001 and *P*=0.02, respectively). During hospitalization period, patients in PPIG were more frequently needed to treat with corticosteroids and anti-cytokine treatment (*P*<0.001 and *P*=0.017, respectively). Other results of the demographic data of both study groups were outlined in the table 1.

Complete blood count (CBC) test results revealed a higher leukocyte, neutrophils, and platelet levels and lower lymphocyte level in PPIG than in NLRG at the first admission of hospitalization (Table 2). Serum ferritin, aspartate aminotransferase (AST), and lactate dehydrogenase (LDH) levels were higher in PPIG (Table 2).

In table 3, pulmonary function test (PFT) results and walked distance in 6MWT were shown. Forced expiratory volume in 1st second (FEV_1, in liters), forced vital capacity (FVC, in liters), DLCO and distance measured after 6MWT were significantly lower in PPIG than in NLRG (Table 3).

Logistic regression analysis showed a statistically significant result for smoking status and age in predicting the risk for pulmonary parenchymal involvement following a severe COVID-19 disease (OR:2.25 [95% CI 1.206-4.200], *P* = 0.011; OR: 1.057 and [95% CI 1.023-1.093], *P* = 0.001, respectively). Age was dichotomized by using a cutoff level as younger than 65 years-old and older and equal than 65 years-old. Also, smoking status was dichotomized as smoker (current or ex-smoker) and non-smoker patients for this analysis (Table 4).

Radiological findings determined by CT of the thorax for all included patients at the end of the first month of hospital discharge were documented in table 5. Bilateral involvement was observed in 96.4% of the cases with pulmonary parenchymal involvement. The most frequently affected lobe was the right lower lobe (98.2%), followed by the left lower lobe (96.7%). The most frequent distribution pattern was peripheral distribution (66.0%). Other first three the most frequent pulmonary parenchymal involvement patterns were ground glass opacities (94.6%), parenchymal bands (77.0) and reticular pattern (52.4%). Other observed patterns and distribution of extent of lung involvement was also shown in table 5.

Within all study population, we diagnosed 122 patients with severely affected interstitial lung diseases (22.1%) who required corticosteroid treatment (CRILD). Mean age of these patients was 65.97±7.38 years and mean age of other corticosteroid unrequired group was 59.19±10.63 years (*P*<0.001). Male gender was more frequent in CRILD (89.3% vs. 51.0%, *P* <0.001). Rate of smokers (current smokers and ex-smokers) were higher in CRILD than corticosteroid unrequired group (P<0.001). As a comorbid disease, ratio of the patients with COPD was higher in CRILD (*P*=0.006). During the hospitalization period, frequency of patients followed-up in intensive care unit was higher in CRILD (*P*<0.001). Other parameters are also outlined in table 6.

Among the laboratory parameters, blood leukocytes, neutrophils, serum ferritin, AST and LDH levels were significantly higher in CRILD compared to the unrequired patients (*P*=0.001, *P*<0.001, *P*<0.001, *P*=0.007 and *P*<0.001, respectively). Blood lymphocyte level was significantly lower in CRILD than in the corticosteroid unrequired group (*P*<0.001) (Table 7).

Pulmonary function test results showed that FEV_1 (%), FVC (L), FVC (%), FEF25-75 (%), and DLCO levels were significantly lower in CRILD group compared to the corticosteroid unrequired patients (*P* <0.001, *P* =0.048, *P* <0.001 and *P* =0.037, respectively). Walking distance tested by 6MWT was also significantly shorter in the corticosteroid required interstitial group (P <0.001) (Table 8).

At the end of the 3rd month of the corticosteroid treatment there was a statistically significant improvement in the pulmonary function test results and the distance in the 6MWT, except FEV1/FVC (Table 9).

Logistic regression analysis showed a statistically significant result for being elderly (≥65 years old), smoking status, male gender and need for $HFNO_2$ treatment in predicting the development of interstitial lung diseases that require a corticosteroid treatment at the end of the first month of discharge following a severe COVID-19 disease (OR:4.756

Table 1. Demographic data and medications used during the hospitalization period in the pulmonary parenchymal involvement group (PPIG) and normal lung radiology group (NLRG)

	PPIG N=391	**NLRG N= 162**	**P**
Age, years, Mean±SD	63.03±9.21	55.73±11.94	<0.001
Gender, N (%)			
Male	259 (66.2)	70(43.2)	<0.001
Female	132 (33.8)	92 (56.8)	
Smoking status, N (%)			
Current smoker	33 (8.4)	9 (5.6)	<0.001
Ex-smoker	160 (40.9)	27 (16.7)	
Non-smoker	198 (50.6)	126 (77.8)	
Smoking consumption, pack-year, Mean±SD	29.44±18.08	23.97±16.70	0.090
Comorbid diseases, N (%)			
Present	274 (70.1)	97 (59.9)	0.020
Absent	117 (29.9)	65 (40.1)	
List of Comorbid Diseases, N (%)			
COPD	36 (9.2)	5 (3.1)	0.012
Asthma	18 (4.6)	13 (8.0)	0.111
Hypertension	157 (40.2)	51 (31.5)	0.055
Heart Failure	12 (3.1)	5 (3.1)	0.991
Coronary heart diseases	66 (16.9)	22 (13.6)	0.334
Arrhythmia	21 (5.4)	6 (3.7)	0.408
Diabetes Mellitus	104 (26.6)	31 (19.1)	0.063
Cerebrovascular event	6 (1.5)	1 (0.6)	0.680
Renal Failure	8 (2.0)	3 (1.9)	1.000
Collagen tissue diseases	12 (3.1)	6 (3.7)	0.702
Thyroid diseases	40 (10.3)	14 (8.6)	0.561
Clinic where the patient hospitalized, N (%)			
Intensive Care Units	143 (36.6)	30 (18.5)	<0.001
Wards	248 (63.4)	132 (81.5)	
Hospital length of stay, days	27.15±13.06	19.77±10.24	<0.001
ICU length of stay, days	14.05±9.52	9.77±7.21	0.021
Supportive Treatment			
Nasal cannula/ mask oxygen	299 (76.5)	97 (59.9)	<0.001
High Flow Oxygen	86 (22.0)	14 (8.6)	<0.001
Non-invasive Mechanical Ventilation	55 (14.1)	12 (7.4)	0.029
Intubation	19 (4.9)	2 (1.2)	0.049
Used medications			
Plaquenil	68 (17.4)	37 (22.8)	0.137
Favipiravir	374 (95.7)	155 (95.7)	0.989
Remdesivir	5 (1.3)	0	0.328
Colchicine	110 (28.1)	38 (23.5)	0.258
Vitamin C	142 (36.3)	51 (31.5)	0.278

Vitamin D	122 (31.2)	44 (27.2)	0.345
Zinc supplementation	37 (9.5)	16 (9.9)	0.880
N-Acetyl Cysteine	66 (16.9)	22 (13.6)	0.334
Corticosteroid Treatment	273 (69.8)	87 (53.7)	<0.001
Anticytokine treatment (Tocilizumab/Anakinra)	27 (6.9)	3 (1.9)	0.017

Abbreviations: COPD: Chronic obstructive pulmonary disease.

Table 2. Laboratory test results for the pulmonary parenchymal involvement group (PPPIG) and normal lung radiology group (NLRG) at outpatient clinic admission at the 1st month of discharge.[¥]

	PPIG	NLRG	P
Leukocytes, cells/mm^3	7850 (2130-31200)	6060 (3780-16160)	**0.003**
Neutrophils, cells/mm^3	6990 (1310-29960)	4730 (1560-13930)	**<0.001**
Lymphocytes, cells/mm^3	720 (270-3090)	1020 (300-2580)	**<0.001**
Hemoglobin, g/dL[*]	13.35±1.87	13.89±1.81	0.285
Platelets, cells/mm^3	280000 (81000-651000)	219000 (115000-615000)	**0.029**
C-reactive Protein, mg/dL	57.0 (0.5-226.0)	46.0 (1.0-211.0)	0.065
Ferritin, ng/mL	648.0 (54.0-4203.0)	267.0 (14.0-2118.0)	**<0.001**
D-Dimer, µg/mL	1.14 (0.10-35.00)	0.90 (0.19-14.00)	0.191
Glucose, mg/dL	135.0 (68.0-518.0)	118.0 (69.0-309.0)	0.083
AST, U/L	47.0 (11.0-754.0)	36.0 (14.0-237.0)	**0.029**
ALT, U/L	42.0 (5.0-440.0)	39.0 (10.0-738.0)	0.705
LDH, U/L	457.0 (174.0-1140.0)	362.0 (195.0-1013.0)	**<0.001**

[¥]Data are Median (min.-max.), unless otherwise indicated.; *Mean ± Standard deviation. Abbreviations: AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: Lactate Dehydrogenase; PPIG: Pulmonary parenchymal involvement group; NLRG: Normal lung radiology group.

Table 3. Pulmonary Function Test (PFT) results and measured walking distance in 6-minute Walking Test (6MWT) of both groups

	PPIG	NLRG	P
FEV_1, lt	2.47±0.71	2.89±0.91	**0.001**
FEV_1, %	89.65±18.21	92.48±15.75	0.647
FVC, L	2.94±0.85	3.37±1.03	**0.017**
FVC, %	85.15±18.81	88.54±15.20	0.616
FEV_1/FVC*	85.26 (41.92-127.00)	85.35 (63.00-99.00)	0.828
FEF_{25-75}, %	90.13±29.45	95.74±31.19	0.307
DLCO, mmol/min/mmHg	16.36±9.35	23.11±14.48	**0.027**
6MWT distance, meters	325.41±123.84	372.25±89.27	**<0.001**

[¥]Data are Mean ± Standard Deviation, unless otherwise indicated; *Median (min-max). Abbreviations: FEV1: Forced Expiratory Volume in 1st second; FVC: Forced Vital Capacity; DLCO: Diffusing Capacity of Lung for Carbon monoxide; 6MWT: 6-minute walking test; PPIG: Pulmonary parenchymal involvement group; NLRG: Normal lung radiology group.

Table 4. Regression analysis for the factors that predicted to be affective on pulmonary involvement status at the end of first month of discharge

	OR	95% CI	*P*
Age	1.057	1.023-1.093	***0.001***
Older age, ≥65 years	0.900	0.393-2.057	0.802
Smoking	2.250	1.206-4.200	**0.011**
Male gender	1.471	0.817-2.647	0.198
Comorbid Condition	1.322	0.728-2.305	0.325
Nasal/mask Oxygen	1.006	0.436-2.319	0.989
$HFNO_2$	1.395	0.647-3.004	0.396
NIMV	0.979	0.426-2.250	0.961
Intubation	2.432	0.439-13.473	0.309
Ferritin	1.000	1.000-1.001	0.191
C-Reactive Protein	0.999	0.995-1.002	0.441
Corticosteroid requirement during hospitalization	1.645	0.781-3.466	0.191

Abbreviations: $HFNO_2$: High Flow Nasal Oxygen; NIMV: Non-invasive Mechanical Ventilation.

Table 5. Distribution of the radiological findings in subjects with pulmonary parenchymal involvement group (PPIG) (N= 391) evaluated by Computed Tomography (CT) of Thorax on first months admission after discharge

	N	%
Laterality		
Right sided	9	2.3
Lefts sided	5	1.3
Bilateral	377	96.4
Lobar distribution		
Right upper lobe	326	83.4
Right middle lobe	326	83.4
Right lower lobe	384	98.2
Left upper lobe	318	81.7
Left lower lobe	377	96.7
Distribution pattern		
Peripheral	258	66.0
Central	6	1.5
Diffuse	127	32.5
Parenchymal bands	301	77.0
Ground glass opacities	370	94.6
Reticular pattern	205	52.4
Pleural thickening	112	28.6
Traction bronchiectasis	109	27.9
Honeycombing	56	14.3
Pleural effusion	3	0.8
Atelectasis	16	2.9
Mosaic attenuation	26	4.1
Pneumothorax	0	0
Extent of Lung Involvement		
0%	162	29.3
5-25%	163	29.5
26-49%	94	17.0
50-74%	115	20.8
≥75%	19	3.4

[95% CI 1.781-12.700], *P* = 0.002; OR: 2.737 [95% CI 1.368-5.475], *P* = 0.004, 4.937[95% CI 2.044-11.924], P <0.001; and OR: 6.116 [95% CI 2.894-12.926], P <0.001, respectively) (Table 10).

Computed tomography findings at the beginning and at the end of the 3rd month of methylprednisolone treatment of 122 subjects were outlined in table 11. Interstitial findings on CT were completely resorbed

Table 6. Demographic data and medications used during hospitalization period in both Corticosteroid required interstitial lung disease group (CRILD) and corticosteroid unrequired group

	CRILD (N=122)	Corticosteroid unrequired group (N=431)	P
Age, years	65.97±7.38	59.19±10.63	**<0.001**
Gender, N (%)			
Male	109 (89.3)	220 (51.0)	**<0.001**
Female	13 (10.7)	211 (49.0)	
Smoking status, N (%)			
Current smoker	19 (15.6)	23 (5.3)	<0.001
Ex-smoker	74 (60.7)	113 (26.2)	
Non-smoker	29 (23.8)	295 (68.4)	
Smoking consumption, pack-year, Mean±SD	29.85±16.19	27.73±19.00	0.382
Comorbid diseases, N (%)			
Present	85 (69.7)	286 (66.4)	0.492
Absent	37 (30.3)	145 (33.6)	
List of Comorbid Diseases, N (%)			
COPD	16 (13.1)	25 (5.8)	**0.006**
Asthma	3 (2.5)	28 (6.5)	0.117
Hypertension	51 (41.8)	157 (36.4)	0.279
Heart Failure	3 (2.5)	14 (3.2)	0.656
Coronary heart diseases	22 (18.0)	66 (15.3)	0.468
Arrhythmia	5 (4.1)	22 (5.1)	0.813
Diabetes Mellitus	32 (26.2)	103 (23.9)	0.597
Cerebrovascular event	0	7 (1.6)	0.357
Renal Failure	2 (1.6)	9 (2.1)	1.000
Collagen tissue diseases	2 (1.6)	16 (3.7)	0.387
Thyroid diseases	11 (9.1)	43 (10.0)	0.772
Clinic where the patient hospitalized, N (%)			
Intensive Care Units	66 (54.1)	107 (24.8)	**<0.001**
Wards	56 (45.9)	324 (75.2)	
Hospital length of stay, days	28.68±10.12	27.06±14.59	**<0.001**
ICU length of stay, days	13.56±6.66	13.19±10.58	0.798

	CRILD (N=122)	Corticosteroid unrequired group (N=431)	P
Supportive Treatment			
Nasal cannula/ mask oxygen	110 (90.2)	286 (66.4)	**<0.001**
High Flow Oxygen	56 (45.9)	44 (10.2)	**<0.001**
Non-invasive Mechanical Ventilation	30 (24.6)	37 (8.6)	**<0.001**
Intubation	11 (9.0)	10 (2.3)	**0.001**
Used medications			
Plaquenil	27 (22.1)	78 (18.1)	0.316
Favipiravir	120 (98.4)	409 (94.9)	0.097
Remdesivir	3 (2.5)	2 (0.5)	0.074
Colchicine	44 (36.1)	104 (24.1)	**0.009**
Vitamin C	45 (36.9)	148 (34.3)	0.602
Vitamin D	41 (33.6)	125 (29.0)	0.327
Zinc supplementation	5 (4.1)	48 (11.1)	**0.020**
N-Acetyl Cysteine	29 (23.8)	59 (13.7)	**0.007**
Corticosteroid Treatment	98 (80.3)	262 (60.8)	**<0.001**
Anticytokine treatment (Tocilizumab/ Anakinra)	13 (10.7)	17 (3.9)	**0.004**

Table 7. Laboratory test results for the corticosteroid required interstitial lung disease group (CRILD) and steroid unrequired group at first admission

	CRILD (N=122)	Corticosteroid unrequired group (N=431)	P
Leukocytes, cells/ mm^3	8290 (2130-174020)	7300 (2270-31200)	**0.001**
Neutrophils, cells/ mm^3	7060 (1310-16120)	5330 (1560-29960)	**<0.001**
Lymphocytes, cells/mm^3	730 (330-1650)	800 (270-3090)	**<0.001**
Hemoglobin, g/ dL	13.62±1.70	13.46±1.93	0.162
Platelets, cells/ mm^3	298000 (81000-518000)	242000 (113000-651000)	0.491
C-reactive Protein, mg/dL	57.00 (3.00-226.00)	61.00 (0.50-282.00)	0.248
Ferritin, ng/mL	819.00 (147.00-4203)	452.00 (14.00-2470.00)	**<0.001**
D-Dimer, µg/mL	1.00 (0.10-256.00)	0.87 (0.10-1250)	0.271
Glucose, mg/dL	135.00 (74.00-475.00)	120.00 (68.00-518.00)	0.163
Aspartate Aminotransferase, AST, U/L	53.00 (17.00-754.00)	39.00 (11.00-445.00)	**0.007**
Alanine Aminotransferase, ALT, U/L	51.00 (12.00-440.00)	39.00 (5.00-738.00)	0.129
Lactate Dehydrogenase, LDH, U/L	471.00 (174.00-1074.00)	400.00 (195.00-1140.00)	**<0.001**

in 35 patients (28.7%). Number of patients having bilateral involvement decreased from 116 (95.1%) to 79 (64.8%). Seventy-two patients out of 118 having ground glass opacities (61.0%) were treated after methylprednisolone treatment. Number of patients having diffuse distribution pattern decreased from 51 (41.8%) to 23 (26.4%). Number of patients having "more than 75% of lung involvement" decreased from 15 (12.3%) to 2 (1.6%). Changes in the other tomography findings were shown in table 11.

Discussion

In the present study, we analyzed 391 patients with "pulmonary parenchymal involvement" (PPIG) and 162 patients with "normal lung radiology" (NLRG) at the end of the first month of discharge following a severe COVID-19 pneumonia. 122 patients among the first group were severely affected subjects who had severe interstitial lung disease with increased symptoms and need to treat with corticosteroid for three months (labeled as CRILD). We identified that pulmonary involvement was more common in males and elder patients (P<0.001 for both). Comorbid diseases (especially, COPD) were frequent in PPIG. Needs to get an oxygen support during hospitalization were also more frequent in PPIG. Frequencies of anti-cytokine and corticosteroid treatment during hospitalization were also higher in PPIG. We also find out a prominent decrease in PFT parameters at the end of the first month of severe COVID-19 disease in PPIG. Being a current or ex-smoker and elderly were associated with a significantly higher risk ratios in predicting the risk for pulmonary parenchymal involvement (OR: 2.250 and

Table 8. Comparison of the Pulmonary Function Test (PFT) results and measured walking distance in 6-minute Walking Test (6MWT) of corticosteroid required interstitial lung disease (CRILD) and corticosteroid unrequired group

	CRILD (N=122)	Corticosteroid unrequired group (N=431)	P
FEV_1, lt	2.43±0.67	2.60±0.81	0.051
FEV_1, %	84.85±17.92	93.43±17.07	<**0.001**
FVC, L	2.89±0.79	3.07±0.95	**0.048**
FVC, %	80.11±17.11	89.25±18.11	<**0.001**
FEV_1/FVC	84.65±9.72	85.72±7.92	0.166
FEF_{25-75}, %	84.66±26.27	94.38±30.96	**0.037**
DLCO, mmol/min/mmHg	14.94±4.18	19.07±12.77	<**0.001**
6MWT distance, meters*	320.00 (55.00-605.00)	380.00 (18.00-619.00)	<**0.001**

¥Data are Mean ± Standard Deviation, unless otherwise indicated; *Median (min-max). Abbreviations: CRILD: corticosteroid required interstitial lung disease; FEV_1: Forced Expiratory Volume in 1st second; FVC: Forced Vital Capacity; DLCO: Diffusing Capacity of Lung for Carbon monoxide; 6MWT: 6-minute walking test.

Table 9. Comparison of the effect of corticosteroid treatment on the pulmonary function test results in corticosteroid required interstitial lung disease group

	CRILD		
	At the beginning of the treatment	At the end of the 3rd month of treatment	P
FEV_1, lt	2.43±0.67	2.49±0.67	<**0.001**
FEV_1, %	84.85±17.92	86.84±17.27	**0.001**
FVC, L	2.89±0.79	3.04±0.82	<**0.001**
FVC, %	80.11±17.11	85.70±14.50	<**0.001**
FEV_1/FVC*	85.26 (41.92-127.00)	83.34 (50.48-107.14)	0.293
FEF_{25-75}, %	84.66±26.27	92.08±25.03	<**0.001**
DLCO, mmol/min/mmHg	14.94±4.18	17.45±4.28	<**0.001**
6MWT distance, meters	325.41±123.84	334.88±108.52	<**0.001**

¥Data are Mean ± Standard Deviation, unless otherwise indicated; *Median (min-max). Abbreviations: CRILD: corticosteroid required interstitial lung disease; FEV_1: Forced Expiratory Volume in 1st second; FVC: Forced Vital Capacity; DLCO: Diffusing Capacity of Lung for Carbon monoxide; 6MWT: 6-minute walking test.

OR: 1.057, respectively). In CRILD group, male, elderly and smoker patients were frequent (P <0.0001, for all). COPD was the most frequent comorbid disease (P=0.006), and hospital length of stay was also longer in CRILD group. PFT results, DLCO levels and 6MWT distance were poorer in CRILD group than the corticosteroid unrequired patients' group. Smoker, male and elderly patients and patients who required $HFNO_2$ support during hospitalization had higher risk factor to be a patient with CRILD (OR: 2.737, OR: 4.937, OR: 4.756, and OR: 2.872, respectively). After a three months of methylprednisolone medication, we showed a very good response on both radiological findings with CT of thorax and PFT results.

There are no clear follow-up recommendations available in routine practice for patients recover from a severe COVID-19 (19). In our hospital, we recommend patients to apply a post-COVID follow-up clinic if they have any pulmonary symptom at the end of the 1st month of their recovery.

Although some improvements in the follow-up of patients and development in the vaccination technology, the number of survivors with pulmonary sequela of COVID-19 that could lead a definite deterioration in the health-related quality of life increased over time (20). We do not have a clear data on how often long-term pulmonary sequela can be seen after recovery from COVID-19, yet. In the light of the experiences obtained from previous coronavirus diseases (SARS-CoV-1 and Middle East Respiratory Syndrome Coronavirus (MERSCoV)),

Table 10. Regression analysis for the prediction of associated factors to have a corticosteroid required interstitial lung disease at the first end of the first month of treatment.

	OR	95% CI	P
Age	1.007	0.962-1.055	0.757
Older age, ≥65 years	4.756	1.781-12.700	**0.002**
Smoking	2.737	1.368-5.475	**0.004**
Male gender	4.937	2.044-11.924	<**0.001**
Comorbid Condition	0.970	0.476-1.973	0.932
Nasal/mask Oxygen	2.872	0.637-12.943	0.170
$HFNO_2$	6.116	2.894-12.926	<**0.001**
NIMV	0.958	0.407-2.256	0.921
Intubation	1.613	0.442-5.892	0.469
Ferritin	1.000	0.999-1.000	0.311
C-Reactive Protein	0.981	0.961-1.002	0.082
Corticosteroid requirement during hospitalization	1.186	0.405-3.475	0.756

Abbreviations: $HFNO_2$: High flow nasal oxygen; NIMV: Noninvasive mechanical ventilation.

Table 11. Changes in the radiological patterns before and after methylprednisolone treatment in the corticosteroid-required interstitial lung diseases population.

	Before Corticosteroid Treatment		After Corticosteroid Treatment	
	N	**%**	**N**	**%**
Laterality				
Right sided	3	2.5	6	4.9
Lefts sided	3	2.5	2	1.6
Bilateral	116	95.1	79	64.8
Lobar distribution				
Right upper lobe	113	92.6	70	57.4
Right middle lobe	111	91.0	73	59.8
Right lower lobe	119	97.5	83	68.0
Left upper lobe	110	90.2	69	56.6
Left lower lobe	117	95.9	78	63.9
Distribution pattern				
Peripheral	67	54.9	61	70.1
Central	4	3.3	3	3.4
Diffuse	51	41.8	23	26.4
Parenchymal bands	94	77.0	75	61.5
Ground glass opacities	118	96.7	46	37.7
Reticular pattern	75	61.5	42	34.4
Pleural thickening	37	30.3	15	12.3
Traction bronchiectasis	42	34.4	11	9.0
Honeycombing	24	19.7	15	12.3
Pleural effusion	1	0.8	0	0
Atelectasis	4	3.3	3	2.5
Mosaic attenuation	15	12.3	9	7.4
Pneumothorax	0	0	0	0
Extent of Lung Involvement				
0%	0	0	35	28.7
5–25%	0	0	70	57.4
26–49%	8	6.6	14	11.5
50–74%	99	81.1	1	0.8
≥75%	15	12.3	2	1.6

persistent pulmonary symptoms and pulmonary sequela to some extent look inevitable following a severe coronavirus pneumonia (21). In the literature, frequency of having pulmonary sequela on CT scan after MERSCoV at the end of 6th weeks and on chest X-ray after SARSCoV-1 at the 3 months were reported as 36% (22, 23). Moreover, deterioration in both PFT parameters and diffusion capacity were also published following previous coronavirus infections (24). During the COVID-19 pandemics, similar pulmonary complications assessed by CT were also reported with different frequencies changing between 30 to 95% (3, 11, 25, 26).

In a study conducted by Wang et al. (25), ground glass opacities were identified in 94% of the cases following the average of 24th day of the discharge. In another study, frequency of tomographic findings of interstitial lung disease including "ground glass opacities, honeycombing pattern, and the parenchymal bands" were reported as 62% at the end of the 6th month following a severe COVID-19 disease (27). In a recently published paper, Meiler et al. (28) conducted a study investigating the CT findings after COVID-19 to ascertain whether they were correlated with residual manifestations of acute viral pneumonia or indicative of a genuine ILD subsequent to COVID-19 infection. The researchers meticulously examined and compared the CT findings during the acute phase of the disease and at least 80 days (mean 134 days) after symptom onset (chronic phase) in a cohort of 29 subjects. Despite the relatively limited number of subjects, the researchers concluded that these findings are more likely associated with the acute phase of the disease rather than post-COVID ILD. In our study, CT findings of interstitial lung disease were observed in 391 out of 553 patients (70.7%) at the end of the 1st month of a severe or critical disease recovery. Three most frequent pattern we observed were ground glass opacities (94.6%), parenchymal bands (77%) and reticular pattern (52.4%). In contrast to the study conducted by Meiler et al. (28), our tomography findings represent earlier findings (1st month of the disease recovery) following the acute disease stage of COVID-19.

In the literature, there are some studies evaluating the associated risk factors for developing the interstitial lung disease after COVID-19 recovery. In these studies, they found that patients receiving mechanical ventilation have a higher risk to develop interstitial lung disease (29,30). Polat et al. reported that older age, male gender, corticosteroid treatment (during the disease process) and hospitalization in ICU had a risk factor changing from 1.03 to 3.8 times to develop interstitial lung disease (11). Logistic regression analysis of our study showed that being older and smoker are associated risk factors (OR: 1.057 and OR: 2250, respectively) for predicting the development of interstitial lung disease

after COVID-19. On the other hand, predicting risk factors for development of severe interstitial lung disease that requires corticosteroid treatment following COVID-19 is associated with being older than 65 years of age, smoker, male gender and need for $HFNO_2$ treatment during hospitalization (OR: 4.756, OR: 2.737, OR: 4.937, and OR: 6.116, respectively).

Although, there is no clear standardized roadmap for pharmacological medications including systemic corticosteroid treatment in post-COVID-19 interstitial lung disease patients, some suggestions for the patients with marked symptoms of exertional dyspnea or acute respiratory failure were published. Additionally, we know that systemic corticosteroid treatment is the cornerstone for the treatment of interstitial lung diseases (31-34). According to this knowledge, we prescribed methylprednisolone to the post-COVID-19 survived patients with symptomatic, hypoxemic and affected with a severe radiological finding at the end of the 1st month of their hospital discharge.

In a study conducted by Myall et al. (35) it was reported that an early initiation of systemic corticosteroid treatment for persistent ILD following COVID-19 within 6 weeks was well tolerated and helpful for the significant improvement in the symptoms, PFT parameters, the distance measured by 6MWT, and radiological findings as well. Similarly, Goel et al. followed 24 patients out of the 49 patients in outpatient department who needed to be prescribed systemic corticosteroid treatment (deflazacort) for 8-10 weeks because of having abnormal radiological findings, resting hypoxia and exertional desaturation. At the end of the study, they reported an improvement in occurrence of symptoms, chest X-ray and CT of thorax findings (3). In another study comparing the effect of high-dose and low-dose prednisolone on post-COVID-19 interstitial lung disease, Dhooria et al. reported no superiority of high dose prednisolone treatment on improving in the clinical, radiological, PFT results and HRQoL parameters in these patient group (36). In our study, we treated 122 patients with prolonged symptoms (dyspnea, cough), desaturation, worsened PFT, exercise capacity and severely affected radiology, then we showed an improvement in clinical (PFT parameters, distance in 6MWT) and radiological findings after oral methyl-prednisolone treatment. These findings were compatible with current literature.

There are some limitations in our study, first one is its retrospective design. Secondly, we do not have radiological or clinical data of corticosteroid unrequired patients with the presence of pulmonary involvement at the end of the 3rd month to compare with the corticosteroid required group. Thirdly, we studied only severe cases, so we cannot generalize our results to all COVID-19 patients. Fourthly, we did not ask patients about vaccination status, so we cannot conclude the effect of vaccination on pulmonary involvement following severe COVID-19 disease. Lastly, we did not collect data for other types of pulmonary involvement like pulmonary embolism.

In conclusion, we evaluated the first-month outcome of severe COVID-19 patients and observed that although it has been passed one month after recovery from COVID-19, complete radiological resolution and symptom-free clinical improvement cannot be achieved. Furthermore, interstitial lung diseases and persistent clinical symptoms were observed. Being older and smoking are found to be the main risk factors for predicting these deteriorations in the future. Moreover, corticosteroid treatment for severely affected cases was found to be effective in improving radiological and functional parameters. Nevertheless, there is a need for a prospective study with a large population to compare the effect of corticosteroids and placebo on these clinical outcomes.

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

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