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Clinical characteristics, imaging, and lung function among patients with persistent dyspnea of COVID-19: a retrospective observational cohort study

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Abstract

The available medical literature on lung function and corresponding clinical characteristics among symptomatic survivors of Corona Virus Disease 2019 (long COVID) is sparse. Primary physicians referred patients who manifested persistent dyspnea months after their index case of infection to a designated clinic. Patients underwent symptom-driven, quality-of-life, physical, and focused respiratory [pulmonary function tests and computed tomography (CT) of the chest] evaluations and were followed over time. In this paper, we present our findings. Patients with abnormal CT imaging were more likely to be of advanced age and to have been hospitalized during their COVID-19 infection. Forced exhaled volume in the first second, forced vital capacity (FVC), total lung capacity, and diffusion capacity of carbon monoxide measurements were found to be significantly lower in patients with abnormal CT imaging. Multivariate regression of clinical characteristics uncovered a significant association between FVC, body mass index, history of hospitalization, and diabetes mellitus. In conclusion, longer-term studies will help further our understanding of the risk factors, disease course, and prognosis of long COVID patients.

Key words: long COVID, chest CT, dyspnea, lung function.

Introduction

It is well-appreciated that infection with SARS-CoV-2 virus, the cause of acute Covid-19 illness, carries substantial morbidity and mortality, and it has also been widely recognized that many patients have persistent symptoms well beyond virologic recovery [1]. Persistence of symptoms has led to the identification of a syndrome of "Long Covid" though there is a lack of consensus about the precise definition of the syndrome, with a resultant lack of clarity about how prevalent long Covid actually is and what the actual characteristics of patients with this syndrome are [2]. Some reports find up to 1 in 10 patients experience persistent symptoms beyond 12 weeks of the acute illness. Long term sequelae of disease has been shown to affect up to 43% of COVID positive cases, and up to half of hospitalized patients. The clinical case definition of long COVID includes

signs and symptoms persisting beyond 12 weeks of the initial infection by Severe Acute Respiratory syndrome caused by Corona virus -2 (SARS CoV-2) [3-5].

Most of the morbidity and mortality related to infection with SARS-CoV-2 is related to the development of pneumonia and the acute respiratory distress syndrome (ARDS) [6]. Dyspnea is a common presenting complaint of patients with so called Post-Acute Sequelae of SARS CoV-2 infection (PASC) [7]. However, the precise characteristics of patients with persistent dyspnea have not been well described in the literature to date.

At our medical center we began a comprehensive post-Covid program in December of 2020. All patients entering the program were initially evaluated by general internists and were then referred if needed to subspecialists for evaluation of particular complaints. All patients with persistent complaints of dyspnea were seen by our pulmonary team. We report here comprehensive clinical, demographic, physiologic and radiographic characteristics of the initial cohort of patients meeting a definition of PASC who were evaluated for complaints of persistent dyspnea. The aim of our study was to document and describe patient characteristics and the trajectory of lung function over time.

Materials and Methods

Data was collected from all patients who visited the post-Covid respiratory program over a period of one year, from December 2020 to December 2021. CT scans were performed at the comparable times as lung function tests points (in the range of 1-2 weeks, considered an inconsequential difference by the authors, given the time course of the disease). As part of the routine clinical evaluation of patients seen in the pulmonary medicine long Covid program, complete pulmonary function testing (spirometry, lung volumes, and diffusing capacity) and chest CT scans were obtained on all patients. Patients' clinical characteristics, symptoms, pulmonary function data and chest computed tomography (CT) results were compiled in a secure database. Vaccination data on patients were not available, since a large part of the data was collected prior to the widespread availability of vaccines to the general population. Chest CT imaging of all patients were independently reviewed and evaluated by the section of Thoracic Radiology. Pulmonary function data was collected using testing from a standardized pulmonary function laboratory and interpreted using the standardized ATS/ERS clinical guidelines for interpretation of pulmonary function testing(1). All patients were over 18 years of age.

The statistical analysis was performed using Stata Statistical software (Statacorp. 2015. Stata Statistical Software: Release 14, College Station, Tx: StataCorp LP). We compared categorical

variables with the chi-squared test, and continuous variables are reported as mean values. Mean values are compared using the student – T test after a normal distribution was detected. A two tailed $p<0.05$ was considered significant. The resulting data are presented in tables and figures to illustrate our findings.

In the analytic portion of our study, an association between baseline patient characteristics, lung function and chest CT findings was carried out using multiple regression analysis.

The overarching aim of the study was to examine the population patients who had persistent dyspnea after their COVID infection. These pateints were subdivided into two cohorts , pateints with normal and abnormal chest imaging, and their lung function was compared to their respective cohorts. Multiple points of comparision was not possible as Long COVID increased in incidence and pulmonologists in the community began assuming care of these patients.

The study was approved by the Institutional Review Board at our institution (IRB ID: 14545).

Results

During the study period, a total of 89 patients with a primary complaint of persistent dyspnea following virologic recovery from SARS-CoV-2 infection were evaluated in the respiratory clinic. The baseline clinical characteristics of these patients are described in Table 1. The study population was predominantly Caucasian with a slight female predominance and most patients were not obese.Only 0.5 % of patients had history of prior lung disease such as asthma or COPD. Among 77 patients that had CT chest imaging available, 32 patients exhibited parenchymal abnormalities that included one or more of the following: ground glass opacities, fibrosis and a mosaic attenuation pattern, while 45 patients exhibited normal CT imaging. These findings are illustrated in Figures 1-3. Abnormalities on chest CT in univariable analysis were associated with a history of diabetes mellitus, hypertension, and initial acute Covid-19 illness requiring hospitalization (Table 2).

Pulmonary function testing was done at comparable time points (in the range of 1-2 weeks of the CT scan) in the disease course after the index COVID infection. Pulmonary function was worse in patients with abnormal lung imaging as compared to those with normal lung imaging (Table 3 and Figure 4). This difference was statistically and clinically significant. Patients with abnormal lung imaging typically demonstrated a restrictive ventilatory pattern, with reduced diffusing capacity. An obstructive ventilatory pattern was generally not observed.

The clinical characteristics of age, gender, ethnicity, BMI, presence of diabetes mellitus, obesity, hypertension, smoking history and history of hospitalization were used as covariates in a multiple

regression analysis predicting their influence on lung function. As described in Table 4, in the multivariable model, only BMI > 30, a history of diabetes mellitus, and a history of hospitalization during the initial episode of acute Covid-19 illness were associated with abnormal lung function (reductions in vital capacity and diffusing capacity).

Several clinical characteristics were associated with the presence of parenchymal lung abnormalities on CT imaging of the chest in the multivariable model (Table 5).

Discussion

We have shown that among patients with post –COVID dyspnea, a significant percentage of patients have abnormal CT imaging findings and impaired pulmonary function. Compared to patients with normal CT imaging, patients with abnormal imaging have significantly lower Forced Exhaled Volume in first second (FEV1), Forced vital Capacity (FVC), Total Lung Capacity (TLC) and Diffusion capacity of Carbon Monoxide (DLCO). The presence of diabetes, hypertension and a history of hospitalization for the acute Covid-19 illness was associated with the presence of abnormal CT imaging and impaired lung function in patients with post COVID dyspnea. This analysis indicates that the syndrome of long Covid, or PASC, as it pertains to persistent pulmonary abnormalities, occurs most often in patients with risk factors for a more severe episode of acute Covid-19 illness to begin with. Hospitalization is generally reserved for patients with at least moderate severity of acute illness, and diabetes and hypertension have been identified in many studies as risk factors for higher morbidity and mortality.

The patterns of abnormality seen on chest imaging in the patients with abnormal lung function seem most often to reflect unresolved ground-glass infiltrates or to be typical of an organizing pneumonia pattern or a pattern suggestive of non-specific interstitial pneumonitis.

Most patients evaluated in our program for dyspnea had normal pulmonary function and normal chest imaging. These patients primarily seem to be experiencing deconditioning [8] (perhaps as a manifestation of a type of post-critical illness syndrome) although a syndrome of dysfunctional breathing has also been described in some PASC patients with prolonged dyspnea despite apparently normal pulmonary function [9-11].

As noted above, the radiographic abnormalities seen on CT imaging of the lungs are most suggestive of organizing pneumonia, a non-specific interstitial pneumonitis pattern, and fibrosis. This is consistent with prior reported radiographic abnormalities in patients recovering from acute SARS-CoV-2 infection [12]. These patterns of tissue injury are familiar and occur in a variety of settings in response to acute lung injury, with or without an infectious trigger.

It is important to note that a majority of patients evaluated in our program had normal pulmonary function and normal chest imaging. This should be reassuring to the many patients with post-Covid dyspnea in the sense that breathlessness, though undeniably real, does not necessarily signal an impairment of lung function or permanent damage to the lungs themselves.

Many of the characteristics that were associated with abnormal lung function and chest imaging post-Covid in our cohort were similar to those reported to be associated with the development of more severe illness during initial acute infection [13-15]. Predictors of the development of long Covid itself are less well defined, though in one interesting study, diabetes did seem to be a risk, along with initial level of viremia, reactivation of prior Epstein-Barr virus infection by SARS-CoV-2 infection, and generation of autoantibodies [13].

We think our report has several strengths. Pulmonary function testing included measurement of lung volumes and diffusing capacity in addition to spirometry. As thromboembolic disease has been reported in many patients with acute Covid-19 illness, the finding of normal diffusion in patients without obvious parenchymal abnormalities is compelling evidence that pulmonary vascular disease is generally also not present, despite the fact that we performed chest CT scanning without the administration of intravenous contrast to specifically exclude thromboembolic disease. In addition, although our report comes from a single center, it also emanates from the area of the country that was hardest hit early in the Covid pandemic. Our hospital established its long Covid program in 2020 and many of the patients described in this report became ill early in the epidemic. We report on consecutive patients seen in our program. Our report has important limitations as well. It comes from a single center, we relied on patient self-report of acute Covid illness, and patients were heterogenous in terms of the treatments they received during their acute Covid episode. Most importantly, we did not have a comparison group of patients recovered from Covid who did not develop PASC. Although this limits us in terms of being able to identify risk factors for long Covid, our main interest was to describe the imaging and physiologic characteristics of such patients, and we have done so. Other investigators have used a variety of approaches to describing risks for long Covid, and our patients in general reflect the risk factors that others have identified.

A major question of course is the natural history and course of patients with long Covid, particularly those with abnormal imaging and lung function. There is an overall paucity of well formulated management guidelines from medical societies for the care of patients with long COVID. The National Institute for Health and Care Excellence (NICE) have released one such guideline recommendations that helps inform practice in the United Kingdom [16]. Owing to the

nebulous nature of the disease, a holistic multi-disciplinary assessment is recommended for making the diagnosis of long COVID. Systematic assessments of organ systems are necessary in an empathetic environment, with an understanding for the risk factors associated with development of long COVID, such as female gender, advanced age and need for hospitalization. Management decisions are best made in a shared decision-making model, with the patient taking on the leading role in self-management of symptoms at home and clinicians offering their best-informed judgement. It is known that during their convalescence, patients increase their utilization of antitussives, bronchodilators, expectorants, and anxiolytics. Wisdom from similar outbreaks in the past (such as SARS CoV-1) have informed us that overall health status of survivors remains lower than the general population up to 2 years out from initial infection, even if lung function and CT imaging improves [17].

Reports on the prognosis of the disease are widely variable [18-23]. Our own experience has been that on average, most patients shown marked improvement at the one-year point, with a trend toward improvement of lung function with time, although not to normal levels.

We have described the clinical characteristics, CT imaging and lung function in patients with persistent dyspnoea post COVID 19. The majority of such patients did not have imaging or physiologic abnormalities. Overall, patients with persistent dyspnoea were more likely to be middle aged Caucasian and female gender. Those patients with abnormal CT imaging were more likely to be of advanced age, needed hospitalization for COVID infection and were more likely to have decreased lung function. Lung function improved over time but did not return to normal levels after 1 year of follow up. Longer term follow up of patients will improve our understanding of the natural progression of disease and help with prognostication models.

Conclusions

What is already known on this topic

The available medical literature on symptomatic survivors of patients with Corona Virus Disease 2019 (long COVID) is sparse but suggests that a significant percentage of patients continue to experience persistent dyspnea long after their index hospitalization.

What this study adds

Our study contributes to a growing body of literature that shows that among patients with post – COVID dyspnea, a significant percentage of patients have abnormal CT imaging findings and impaired pulmonary function. Predictably, compared to patients with normal CT imaging, patients

with abnormal imaging have significantly lower Forced Exhaled Volume in first second (FEV1), Forced vital Capacity (FVC), Total Lung Capacity (TLC) and Diffusion capacity of Carbon Monoxide (DLCO).

How this study might affect research, practice, or policy

Our study is an effort to describe the scope of the disease. Future research directed towards mechanisms of organ injury will be invaluable in formulating therapeutic options for patients with long COVID.

Abbreviation List:

COVID - Corona Virus Disease 2019
SARS CoV-2 - severe acute respiratory syndrome caused by Corona virus -2
ARDS - acute respiratory distress syndrome
CT - computed tomography
NICE - National Institute for Health and Care Excellence
FEV1 - forced exhaled volume in first second
FVC - forced vital capacity
TLC - total Lung Capacity
DLCO - diffusion capacity of carbon monoxide

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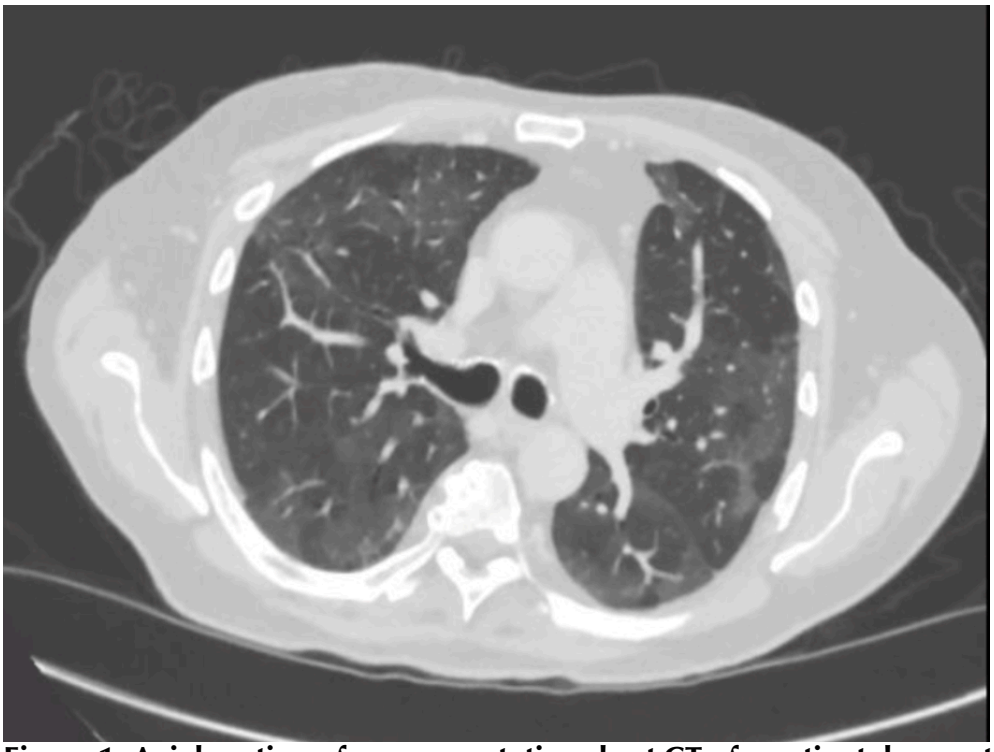

Figure 1. Axial section of a representative chest CT of a patient demonstrating the typical finding of scattered ground glass opacities affecting all lobes.

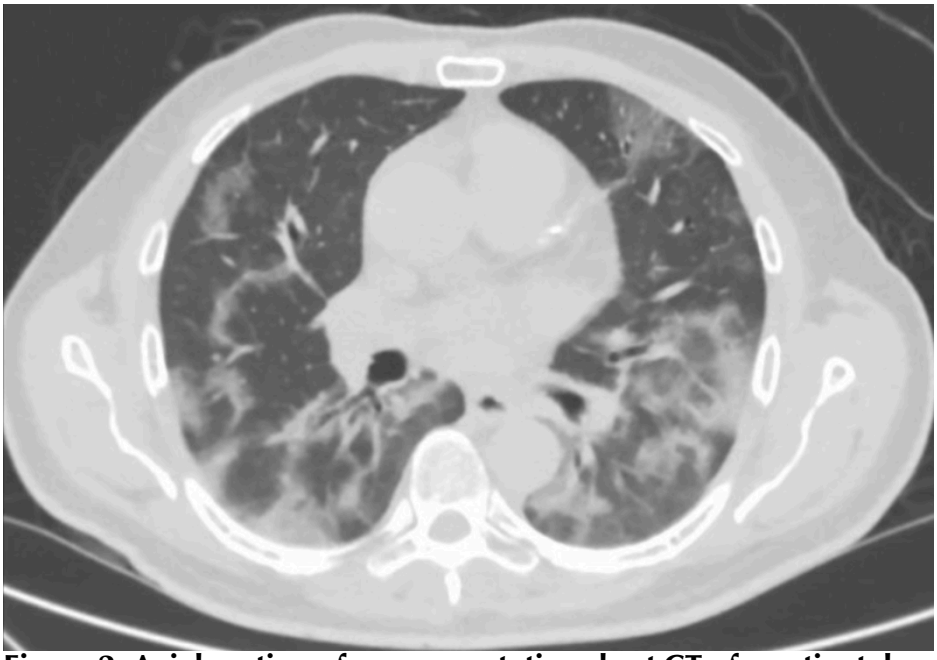

Figure 2. Axial section of a representative chest CT of a patient demonstrating the typical finding of scattered ground glass opacities but with new areas of consolidation affecting predominantly lower lobes.

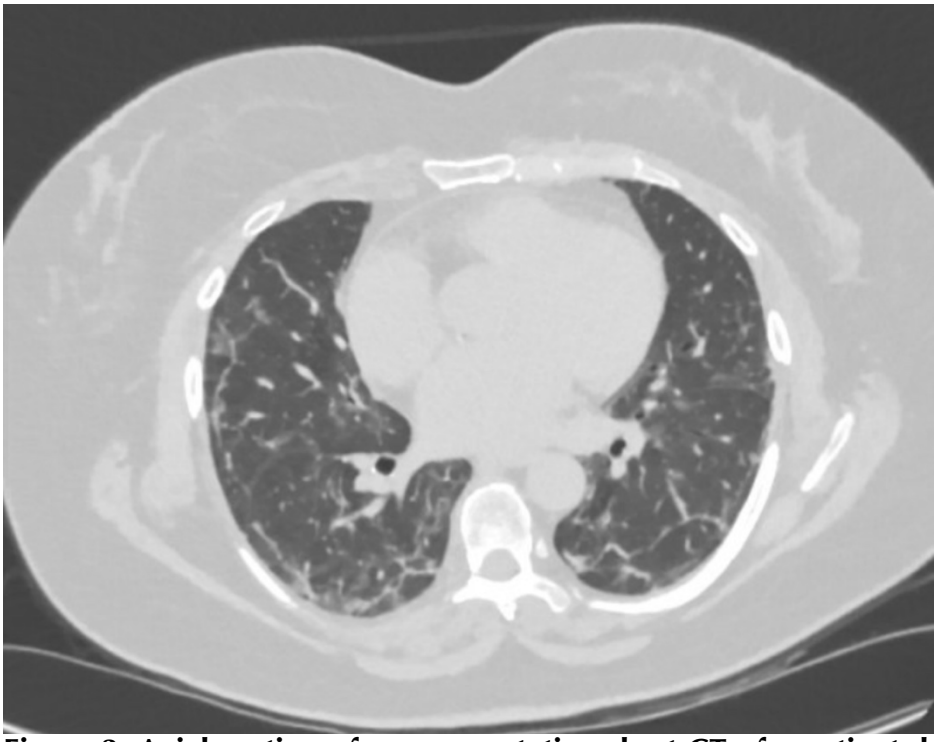

Figure 3. Axial section of a representative chest CT of a patient demonstrating scattered areas of sub-pleural fibrosis with resolution of the majority of ground glass opacities and consolidations over time.

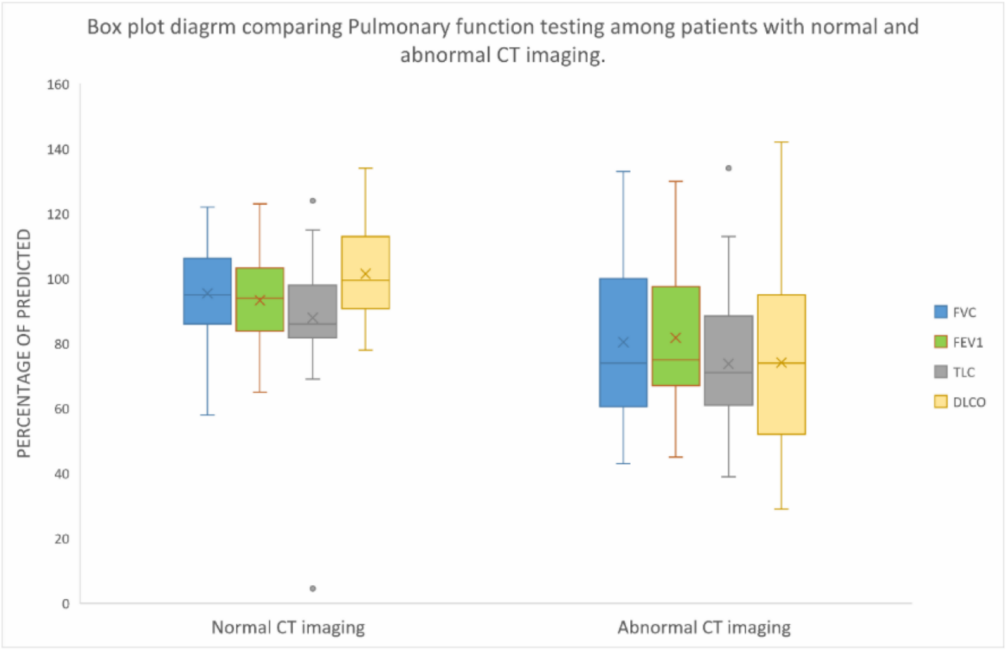

Figure 4. Box plot diagram comparing pulmonary function testing among patients with normal and abnormal CT imaging.

Table 1. Baseline characteristics of patients in the study.

Variable	**N (%)**
Age (years+/- SD)	55 +/- 14.5
Gender, female	52 (58%)
Ethnicity	
Caucasian	49 (55%)
Black	14 (16%)
Hispanic	15 (17%)
Other	9 (11%)
Body mass index (Mean +/- SD)	30.9 +/- 6.3
<30	54 (61%)
30-39.9	30 (34%)
>40	5 (5%)
Comorbidities	
Diabetes mellitus	15 (16%)
Hypertension	25 (28%)
Smoking history	33 (37%)
Obesity	35 (39%)
Immunocompromised	8 (9%)
Number of patients hospitalized	28 (32%)

SD, standard deviation.

Table 2. Patient characteristics with normal CT imaging compared to abnormal CT imaging.

Variable	Patients with Normal CT Imaging	Patients with Abnormal CT Imaging	Chi Squared P value
Number of patients	45	32	
Age (Years+/- SD)	48 +/- 12	65 +/- 13	
Gender, female	35(78%)	17 (53%)	
Ethnicity			
Caucasian	30 (67%)	16(50%)	
Black	7 (16%)	6 (19%)	
Hispanic	7 (16%)	7 ((22%)	
Other	1 (2%)	1 (3%)	
Body Mass Index (Mean +/- SD)	31+/-6	31+/-7	P=0.06
<30	17 (38%)	19 (59%)	
>30	28 (62%)	13 (41%)	
Comorbidities			
Diabetes Mellitus	3 (6%)	12 (38%)	P<0.001
Hypertension	11 (24%)	15 (47%)	P= 0.04
Smoking History	19 (42%)	11 (34%)	P=0.48
Obesity	30 (67%)	26 (81%)	P=0.15
Immunocompromised	3 (7%)	5 (16%)	
Patients hospitalized	6 (13%)	16 (50%)	P<0.001
Treatment received	13 (29%)	22 (69%)	P<0.001
Dexamethasone	6 13%	10 31%	0.056
Remdesivir	6 13%	9 28%	
Symptoms & Signs			
Dry cough	13 29%	10 31%	
Shortness of breath	41 91%	26 81%	
Exertional dyspnea	36 80%	24 75%	
Crackles on auscultation	0	0	
Treatment	1	9	
Corticosteroids	16	8	
Symptomatic			

SD, standard deviation.

Table 3. Lung function of patients with normal CT imaging compared to those with abnormal CT imaging.

Variable	Patients with Normal Imaging	Patients with Abnormal Imaging	P value
Number of patients	45	32	
Time after initial covid infection (months +/- SD)	7+/-5	6+/-4	
Mean FEV1 (95% Confidence Interval)	93 (88-98)	82(59-105)	0.04
Mean FVC (95% CI)	95(90-100)	80 (70-90)	0.01
Mean TLC (95% CI)	87 (81-95)	75 (66-84)	0.02
Mean DLCO % (95% CI)	101 (96-107)	73 (63-83)	0.00001
Mean 6MWT (95%CI)	363 (329-397)	348 (299-398)	0.6

*FEV1, FVC and TLC were measured in Liters and expressed as a percentage of their expected based on ATS criteria and NHANES III reference values, DLCO was measured in ml/min/mm of Hg and expressed as a percentage of expected 6MWT – six minute walk test was measured in meters.

Table 4. Multi-variate regression analysis of patient characteristics significantly associated with abnormal lung function.

Variable	Dependent variables	P value
Forced vital Capacity	Body Mass index Diabetes mellitus Hospitalization history	0.001 0.003 0.0001
Diffusion Capacity of Carbon Monoxide (DLCO)	Diabetes mellitus	0.003
*No statistically significant associations or predictors were found to influence Total Lung Capacity.		

Table 5. Multi-variate regression analysis of patient characteristics associated with abnormal lung imaging on CT scans.

Clinical Characteristics	P value
Age	0.0002
Diabetes mellitus	0.01
Hospitalized	0.05
Hypertension	0.53
Obesity	0.35
Immunocompromised state	0.11
Smoking history	0.45
Intubation	0.25
Body mass index	0.62