RE: Association of Abnormal Pulmonary Vasculature on CT Scan for COVID-19 Infection with Decreased Diffusion Capacity in Follow Up: a retrospective cohort study.

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Abstract

Background: Coronavirus Disease 2019 (COVID-19) is a highly contagious respiratory viral illness causing pneumonia and systemic disease. Abnormalities in pulmonary function after COVID-19 infection have been described. The determinants of these abnormalities are unclear. We hypothesized that inflammatory biomarkers and CT scan parameters at the time of infection would be associated with abnormal gas exchange at short term follow-up.

Methods: We studied subjects who were hospitalized for COVID-19 pneumonia and then discharged. Serum inflammatory biomarkers, CT scan, and clinical characteristics were assessed during the hospitalization. CT images were evaluated by Functional Respiratory Imaging with automated tissue segmentation algorithms of the lungs and pulmonary vasculature. Volumes of the pulmonary vessels that were $\leq 5\text{mm}$ (BV5), 5-10mm (BV5_10), and $\geq 10\text{mm}$ (BV10) in cross sectional area were analyzed. Additionally, the amount of opacification on CT (i.e. ground glass opacities) was quantified in each patient. Pulmonary function tests were performed 2-3 months after discharge. We divided subjects into those with a DLCO $<80\%$ predicted (Low DLCO) and those with a DLCO $\geq 80\%$ predicted (Normal DLCO) based on these pulmonary function tests.

Results: 38 subjects were included in our analysis. 31 out of 38 (81.6%) subjects had a DLCO $<80\%$ predicted. Hemoglobin, inflammatory biomarkers, spirometry and lung volumes were similar between groups. CT opacification and BV5 were not different between groups, but both Low and Normal DLCO groups had lower BV5 measures compared to healthy controls. BV5_10 and BV10 measures were higher in the Low DLCO group compared to the Normal DLCO group. Both BV5_10 and BV10 in the Low DLCO group were greater compared to healthy controls. BV5_10 was independently associated with DLCO $<80\%$ in multivariable logistic regression (OR 1.29, 95% CI 1.01, 1.64). BV10 negatively correlated with DLCO% predicted ($r=-0.343$, $p=0.035$).

Conclusions: Low DLCO is common after COVID-19 infection, and abnormalities in pulmonary vascular volumes at the time of hospitalization are independently associated with a low DLCO. There was no relationship between inflammatory biomarkers during hospitalization and DLCO. These findings suggest that pulmonary vascular abnormalities during hospitalization with COVID-19 might have long-lasting effects on pulmonary function.

Introduction

Coronavirus Disease 2019 (COVID-19) is a highly contagious respiratory viral illness causing pneumonia, abnormal coagulation, and systemic disease. As of February 2021, it is responsible for over 26.5 million infections and more than 450,000 deaths in the United States. The disease spectrum is vast, with some people having mild illness whereas others develop acute respiratory distress syndrome (ARDS), multisystem organ failure, and death. It is characterized by sometimes severe and life-threatening systemic inflammation and immune dysregulation. [1]

A hallmark feature of COVID-19 infection is dyspnea and hypoxemia. Much of the dyspnea can be explained by the degree of pneumonia present on imaging, but not uncommonly there is a disconnect between the degree of hypoxemia and abnormal lung parenchyma. [2] It has been shown in an autopsy series that those that died of COVID-19 had widespread thrombosis and microangiopathy of the pulmonary vessels [3] suggesting that pulmonary vascular disease plays an important role in the pathophysiology of hypoxemia in the infected patient. Additionally, an unusually high prevalence of venous thromboembolism has been reported in several studies. [4, 5]

Although COVID-19 causes an acute illness, it is now recognized that illness can be prolonged in up to 62% of those infected. [6] Abnormalities in pulmonary function after COVID-19 infection have been described, including restrictive impairments and reductions in diffusing capacity of carbon monoxide (DLCO). [7–11] The determinants of these abnormalities are unclear. One study found an association with D-dimer measured during acute illness with abnormal DLCO at follow-up. [12] A previous study demonstrated that abnormalities in pulmonary vascular volumes as measured by automated segmentation algorithm were associated with COVID-19 infection. [13, 14] We hypothesized that inflammatory biomarkers and CT scan measures of blood vessels at the time of infection would be associated with abnormal gas exchange at follow-up.

Methods

We studied subjects who were hospitalized for COVID-19 pneumonia at a single center (Temple University Hospital, Philadelphia, Pennsylvania, USA) and then discharged between March to July 2020. Those with pre-existing lung disease (except asthma) or known reduced DLCO prior to COVID-19 infection were excluded from our analysis (See Fig. 1 for CONSORT Diagram). Serum inflammatory biomarkers (including C-reactive protein [CRP], D-dimer, Ferritin, Fibrinogen, Lactate Dehydrogenase [LDH]), CT scan, and clinical characteristics were assessed during the index hospitalization. Serum inflammatory markers were assessed daily while in the hospital. For the sake of our analysis, admission hemoglobin and peak values of the inflammatory biomarkers were compared. Pulmonary function tests, including spirometry, lung volumes, DLCO and 6-minute walk tests were performed at 2–3 months after discharge according to the American Thoracic Society/European Respiratory Society Guidelines. [15] Normal values were calculated in usual fashion using NHANES III normative values. [16] We divided subjects into those with a DLCO < 80% predicted (Low DLCO) and those with a DLCO $\geq$ 80% predicted (Normal DLCO) based on these follow-up pulmonary function tests. This study was approved by the Institutional Review Board at Temple University.

Imaging

Because the patient scans were acquired in the course of clinical care and without a standardized protocol, slice thickness varied between 0.625 mm and 3.0 mm. The methods of CT analysis of the pulmonary blood volumes have been previously described. [13] Briefly, CT images at the time of hospitalization (hospital day 0 or 1) were evaluated by Functional Respiratory Imaging (FRI; FLUIDDA, NV,

Belgium) which uses (deep learning trained) automated tissue segmentation algorithms to produce quantitative measures of pulmonary tissue. Measures of the pulmonary vascular volume include the total vascular volume and the vascular volume of the pulmonary vessels grouped using two thresholds, ultimately resulting in three categories: vessels less than 5 mm² in cross sectional area (BV5), vessels bigger than 5 mm² and less than 10 mm² in cross sectional area (BV5_10), and finally vessels bigger than 10 mm² in cross sectional area (BV10). These volumes are the combined volumes of the intrapulmonary arteries and veins. Additionally, the amount of opacification on CT was quantified using a deep-learning algorithm trained to quantify the total extent of consolidation, ground glass opacity, edema, reticular disease and crazy paving.

Statistics

All statistical analyses were performed using SPSS v25 (IBM, Armonk, New York, USA). The two DLCO groups were compared with either unpaired t tests or chi squared tests for continuous or categorical variables, respectively. Levene's test was used to assess equality of variances for the independent variables of interest between the two groups. Fisher's exact tests were used for categorical variables if counts per group were less than 5. Mann Whitney U tests were conducted on non-normally distributed continuous data. Blood volumes were compared between the low DLCO group, normal DLCO group, and a previously analyzed cohort of 107 healthy controls without COVID-19 infection [13] using one way ANOVA with post hoc analysis for multiple comparisons using Bonferroni tests. Correlations between pulmonary vascular volumes and DLCO% predicted were calculated with Pearson's test. Multivariable logistic regression for DLCO < 80% predicted was performed with vascular volumes (individual vascular volumes tested in separate models to reduce collinearity) as the independent variables of interest with demographics, smoking status, lung volumes and hemoglobin as covariates. A p value of < 0.05 was considered statistically significant.

Results

Baseline subject characteristics and follow-up pulmonary function tests are presented in Table 1. There were 12 subjects from the initial cohort of 99 subjects that had pulmonary function tests prior to Covid infection, and 8 were excluded due to low DLCO. There were 38 subjects who had pulmonary function tests during follow-up and CT scans on hospital admission. 31 (81.6%) of the cohort had low DLCO, and 7 had normal DLCO. The groups were similar in terms of demographics, body mass index, height, smoking status, and comorbidities. Pulmonary function tests were performed 76.5 ± 35.1 days after the first day of hospitalization. Spirometric measures (FEV₁, FVC, FEV₁/FVC) and lung volumes (TLC) were similar between groups. Both DLCO and DLCO adjusted for alveolar volume (DLCO/VA) were lower in the Low DLCO group.

Table 1
Baseline Characteristics and Follow-up PFTs.

	Normal DLCO	Low DLCO	p
	n = 7	n = 31	
Age (years)	55.1 ± 15.9	59.8 ± 12.4	0.399
Gender (male)	3 (42.9)	16 (51.6)	0.676
Race			0.292
Caucasian	0 (0)	3 (9.7)	
African American	2 (28.6)	18 (58.1)	
Hispanic	4 (57.1)	8 (25.8)	
Other	1 (14.3)	2 (6.4)	
Height (inches)	64.3 ± 2.4	66.6 ± 3.9	0.138
BMI (kg/m ²)	39.2 ± 9.5	33.9 ± 5.6	0.190
Smoking Status			0.585
Nonsmoker	5 (71.4)	18 (57.6)	
Current Smoker	0 (0)	4 (12.9)	
Former Smoker	2 (28.6)	9 (29.0)	
HTN	4 (57.1)	22 (71.0)	0.656
DM	4 (57.1)	13 (41.9)	0.678
CKD	1 (14.3)	4 (12.9)	1.000
CAD	2 (28.6)	3 (9.7)	0.223
CHF	0 (0)	9 (27.9)	0.164
ESRD	0 (0)	1 (3.2)	1.000
Asthma	0 (0)	5 (16.1)	0.561
Follow Up			
Days after Hosp	74.4 ± 41.8	74.9 ± 34.5	0.997

Definition of Abbreviations: DLCO = diffusing capacity of carbon monoxide; BMI = body mass index; HTN = hypertension; DM = diabetes mellitus; CKD = chronic kidney disease; CAD = coronary artery disease; CHF = congestive heart failure; ESRD = end stage renal disease; mMRC = modified Medical Research Council; 6MWD = 6-minute walk distance; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; TLC = total lung capacity; DLCO/VA = DLCO adjusted for alveolar volume

	Normal DLCO	Low DLCO	p
mMRC dyspnea score	0.86 ± 0.90	1.40 ± 1.13	0.246
6MWD (feet)	984 ± 206	960 ± 249	0.834
FEV ₁ (%predicted)	88.4 ± 13.3	84.7 ± 19.9	0.644
FVC (%predicted)	88.0 ± 15.2	85.2 ± 19.2	0.724
FEV ₁ /FVC	79.7 ± 6.9	77.8 ± 6.9	0.522
TLC (%predicted)	80.3 ± 15.0	81.1 ± 15.1	0.534
DLCO (%predicted)	89.9 ± 12.6	55.5 ± 12.2	< 0.0001
DLCO/VA (%predicted)	111.7 ± 13.1	82.6 ± 17.4	< 0.0001
Definition of Abbreviations: DLCO = diffusing capacity of carbon monoxide; BMI = body mass index; HTN = hypertension; DM = diabetes mellitus; CKD = chronic kidney disease; CAD = coronary artery disease; CHF = congestive heart failure; ESRD = end stage renal disease; mMRC = modified Medical Research Council; 6MWD = 6-minute walk distance; FEV ₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; TLC = total lung capacity; DLCO/VA = DLCO adjusted for alveolar volume			

Serum inflammatory markers, medical therapies, oxygen requirements and needs for respiratory support, and CT measures of opacification and vascular volumes are presented in Table 2. Of note, admission hemoglobin and peak levels of ferritin, C-reactive protein, LDH, D-dimer, and fibrinogen were similar between the two groups. Peak oxygen requirements were also similar between groups. More patients in the Low DLCO group required advanced respiratory support (high flow nasal cannula or invasive mechanical ventilation) but the difference between groups was not statistically significant. The number of patients in each group receiving various medical therapies, including corticosteroids, remdesivir, and monoclonal antibodies, were similar. All patients received at least low dose low molecular weight heparin for venous thromboembolism prophylaxis. Length of stay was similar between groups. 2 patients were diagnosed with a pulmonary embolism and 1 patient with a lower extremity deep venous thrombosis in the Low DLCO group, but none were diagnosed with venous thromboembolism in the Normal DLCO group. However, the incidence of venous thromboembolism was not statistically different.

Table 2
Group Characteristics of Hospitalization.

	Normal DLCO	Low DLCO	p
	n = 7	n = 31	
Labs			
Admission Hgb (g/dL)	13.6 ± 0.99	12.87 ± 1.63	0.292
Peak Ferritin (ng/mL)	247 ± 190	656 ± 751	0.138
Peak CRP (mg/dL)	8.4 ± 6.5	7.1 ± 5.0	0.597
Peak LDH (U/L)	242 ± 58	348 ± 149	0.075
Peak D-dimer (ng/mL)	538 ± 208	4676 ± 10417	0.268
Peak Fibrinogen (mg/dL)	646 ± 173	486 ± 189	0.267
Medical Therapies			
Corticosteroids	1 (14.3)	12 (38.7)	0.115
Remdesivir	1 (14.3)	7 (22.6)	0.255
Anakinra	0 (0)	1 (3.2)	0.451
IVIG	0 (0)	1 (3.2)	0.451
Tocilizumab	0 (0)	4 (12.9)	0.327
CT Measures			
BV5 (mL)	79.9 ± 39.9	81.0 ± 39.2	0.943
BV5_10 (mL)	42.6 ± 6.9	54.2 ± 13.3	0.005
BV10 (mL)	93.0 ± 33.4	138.1 ± 53.1	0.001
Opacification (mL)	89.8 ± 90.8	221.7 ± 272.3	0.218
Hospital Characteristics			
LOS (days)	4.43 ± 1.51	6.26 ± 5.96	0.429
Peak O2 Req (L/min)	0.57 ± 0.98	5.66 ± 12.55	0.433
Room Air	5 (71.4)	17 (54.8)	
NC O2	2 (28.6)	8 (25.8)	

Definition of Abbreviations: DLCO = diffusing capacity of carbon monoxide; Hgb = hemoglobin; CRP = C-reactive protein; LDH = lactose dehydrogenase; IVIG = intravenous immunoglobulin; LOS = length of stay; NC = nasal cannula; HFNC = high flow nasal cannula; IMV = invasive mechanical ventilation; PE = pulmonary embolism; DVT = deep venous thrombosis

	Normal DLCO	Low DLCO	p
HFNC O2	0 (0)	4 (12.9)	0.650
IMV	0 (0)	2 (6.5)	1.000
New PE	0 (0)	2 (6.5)	1.000
New DVT	0 (0)	1 (3.2)	
Definition of Abbreviations: DLCO = diffusing capacity of carbon monoxide; Hgb = hemoglobin; CRP = C-reactive protein; LDH = lactose dehydrogenase; IVIG = intravenous immunoglobulin; LOS = length of stay; NC = nasal cannula; HFNC = high flow nasal cannula; IMV = invasive mechanical ventilation; PE = pulmonary embolism; DVT = deep venous thrombosis			

Figure 2 is an example of pulmonary vessels according to size and shows the striking difference between a patient with a normal diffusion compared to one with low diffusion. CT slice thickness was not different between groups. The quantity of opacification on CT scan was not different between groups (221.7 ± 272.3 vs. 89.8 ± 90.8 mL in the Low DLCO group and Normal DLCO group, respectively, $p = 0.218$). BV5 was not different between Low and Normal DLCO groups (81.0 ± 39.2 vs. 79.9 ± 39.9 mL, $p = 0.943$), but BV5 in both Low and Normal DLCO groups was lower than the healthy control group (137.0 ± 24.9 mL, $p < 0.0001$ for both Low and Normal DLCO groups, respectively). See Fig. 3. However, BV5_10 was greater in the Low DLCO group compared to the Normal DLCO group (54.2 ± 13.3 vs. 42.6 ± 6.9 mL, $p = 0.005$), and BV10 was also greater in the Low DLCO group (138.1 ± 53.1 vs. 93.0 ± 33.4 mL, $p = 0.001$). Both BV5_10 and BV10 in the Low DLCO group were greater than the healthy controls ($p < 0.0001$ for both) but there was no difference between the Normal DLCO group and healthy controls. See Fig. 4. BV5_10 was independently associated with DLCO $< 80\%$ in multivariable logistic regression (OR 1.29, 95% CI 1.01, 1.64, $p = 0.041$). BV10 tended to have an independent association with DLCO $< 80\%$ but it was not statistically significant (OR 1.06, 95% CI 1.00, 1.13, $p = 0.072$). However, BV10 had a statistically significant negative correlation with DLCO% predicted ($r = -0.343$, $p = 0.035$). See Fig. 5.

Discussion

We analyzed the impact of COVID-19 pneumonia on follow-up pulmonary function tests. We identified factors during hospitalization that were related to abnormalities in lung diffusion capacity at the time of follow-up. The fact that there was no evidence of restrictive lung disease or anemia in our cohort suggests that the underlying pathophysiological mechanism relates to abnormal pulmonary vascular and thrombotic issues instead of persistence of pulmonary parenchymal abnormalities. Several previously published reports indicate that the majority of ground glass opacities clear in a short period of time after COVID 19 pneumonia. [17, 18] A case series of 149 patients [19] showed near complete radiological resolution on CT 3 weeks after discharge but there was faster clearing of parenchymal abnormalities in younger patients.

Several previous studies of patients that had COVID-19 pneumonia have shown diffusion capacity to be the most common pulmonary function test abnormality at follow-up. A prospective longitudinal cohort from the Netherlands found decreased diffusion to be the most frequent abnormality in 101 patients.[11] Similar findings were seen in two retrospective series from China. [7, 12] In a smaller series from Germany with 33 patients, decreased diffusing capacity was seen in 77% of patients and it was the only significant abnormality on complete pulmonary function tests.[20] Likewise, in 110 patients discharged after COVID-19 pneumonia, decreased diffusion was seen in 47.2% of cases, being more common than obstruction or restriction.[8] More recently, a systematic review and meta-analysis concluded after COVID-19 pneumonia the most important of the pulmonary function tests affected was diffusing capacity of carbon monoxide. [21]

Although we did not find a difference between groups in D-dimer levels, it has been reported. The relation between D-dimer elevation during hospitalization and decreased diffusing capacity in follow-up has been previously described by Zhao et al. [12] in a series with 55 patients. In the multivariable logistic regression model it was found that higher level of D-dimer at admission were associated with follow up DLCO < 80% predicted ($p = 0.031$, OR 1.066, 95% CI 1.006 to 1.129). Another study from Spain [22] with a larger cohort also found a relationship between maximum D-dimer levels and lower diffusing capacity in subsequent pulmonary function testing. Our report used peak D-dimer during hospitalization instead of D-dimer at admission. D-dimer levels during hospitalization have shown to have a relationship with mortality, thromboembolic events and need for invasive mechanical ventilation. [23]

Pulmonary vascular abnormalities in COVID 19 pneumonia have been widely reported. Using CT pulmonary angiography and dual energy CT, a retrospective series of 39 mechanically ventilated patients with COVID 19 pneumonia [24] found dilated peripheral vessels (vascular tree-in-bud pattern) and arterial filling defects in the majority of cases. Very similar findings were seen in another retrospective study of 85 patients [25]; their pulmonary dual energy CT angiography revealed a significant number of pulmonary ischemic areas even in the absence of visible pulmonary arterial thrombosis, raising the possibility of micro thrombosis associated with COVID-19 pneumonia.

Other chronic pulmonary conditions have also shown pulmonary vascular remodeling; using CT chest for reconstructions of the pulmonary vasculature in patients with chronic thromboembolic pulmonary hypertension (CTEPH), compared to healthy controls there was loss of the distal vessels, dilation of the proximal vessels and increased vascular tortuosity. [26] In a study of smokers,[27] loss of the small blood vessels ($< 5 \text{ mm}^2$) was found. The magnitude of the changes was correlated to the clinical severity of their lung disease.

Regarding the assessment of small pulmonary blood vessels in our cohort, the paper by Lins et al. [13] has already shown that patients with COVID-19 pneumonia compared to healthy individuals seem to have redistribution in the blood volume with decrease in blood vessels with an area less than 5 mm^2 and an increase in the blood vessels with an area of 5 to 10 mm^2 and more than 10 mm^2 . This has been commonly interpreted as evidence of elastic pulmonary arterial dilation proximal to areas of increased

pulmonary vascular resistance downstream; the dilation of vessels more proximal than those smaller than 5 mm² leads to an increase in BV5_10 and 10 and a reduction in BV5. This may be suggestive of persistent dysregulation of pulmonary vascular tone which could contribute to reduced diffusing capacity.

Our data show that COVID-19 pneumonia patients with pulmonary vascular abnormalities have an associated low diffusing capacity in follow-up pulmonary function tests. This has biologic plausibility, considering the profound pathologic changes seen in lungs obtained during autopsy with patients who died from COVID-19 pneumonia. [3] Changes include severe endothelial injury with disruption of cell membranes, capillary microthrombi and new vessel growth with widespread angiogenesis. Additionally, in a recent study, [28] 83% of patients with severe COVID-19 pneumonia have evidence of intrapulmonary right to left shunt, which is more evidence of profound vascular anomalies. Our findings support that the presence of pulmonary vascular remodeling in COVID-19 pneumonia patients can predict future isolated impairment in diffusing capacity.

Our study has several limitations. Firstly, our cohort is small and our data were retrospectively collected. Secondly, due to several logistic reasons we did not see all of our patients at the same time after discharge in a protocol driven fashion. Ideally, the pulmonary function tests would have been done at the same time after diagnosis of COVID-19 pneumonia to avoid confounding by the natural history and progression of COVID-19 related pulmonary disease. Thirdly, the elevation of serum D-dimer levels during hospital admission could have impacted treatment decisions that might have influenced subsequent pulmonary function testing and diffusing capacity. Finally, many of the patients hospitalized at our institution were lost to follow-up for many reasons (unable to contact, discharge to long-term care facility after hospitalization, death, etc.). This may have skewed our data towards less sick patients.

Conclusion:

In conclusion, our findings suggest that COVID-19 pneumonia can result in pulmonary vascular abnormalities that may have long-lasting effects on gas exchange even after resolution of acute illness. This phenomenon may contribute to the pathophysiology of persistent symptoms after COVID-19 infection. Further study regarding the influence of pulmonary vascular volumes on short and long term COVID-19 outcomes is warranted.

Declarations

Ethics approval and consent to participate: This study was approved by the Institutional Review Board at Temple University. Protocol Number 26984.

Consent for publication: Not required

Availability of data and materials: All the datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request

Competing Interests: Over the past three years, VK reports personal fees from Gala Therapeutics, the ABIM, AstraZeneca, and Boehringer Ingelheim outside the submitted work; ML, JDB, BL have received monies from Fluida, Inc; IO, MD, RG, FJ, MEVS, DS have no competing interests to declare.

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Author Contributions: VK, DS conceived and designed the analysis plan, performed the data analysis and contributed significantly to the writing of the manuscript; IO, MD, FJ, MEVS, RG generated much of the data and contributed significantly to the writing of the manuscript; ML, JDB, BL conducted the CT scan analysis and contributed significantly to the writing of the manuscript; contributed significantly to the data analysis and the writing of the manuscript.

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Abbreviations

ANOVA: Analysis of variance

ARDS: Acute respiratory distress syndrome

BV5: Pulmonary blood vessels $\leq 5\text{mm}$

BV5_10: Pulmonary blood vessels 5-10mm

BV10: Pulmonary blood vessels $\geq 10\text{mm}$

CI: Confidence Interval

COVID-19: Coronavirus Disease 2019

CT: Computed Tomography

CTEPH: chronic thromboembolic pulmonary hypertension

CRP: C-reactive protein

DLCO: Diffusion capacity of carbon monoxide

FEV1: Forced expiratory volume in 1 second

FRI: Functional Respiratory Imaging

FVC: Forced vital capacity

LDH: Lactate Dehydrogenase

NHANES: National Health and Nutrition Examination Survey

OR: Odds ratio

R: Pearson product-moment correlation coefficient

SPSS: Statistical Package for the Social sciences

TLC: Total Lung Capacity

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Tables

Table 1. Baseline Characteristics and Follow-up PFTs.

	Normal DLCO n=7	Low DLCO n=31	p
Age (years)	55.1±15.9	59.8±12.4	0.399
Gender (male)	3 (42.9)	16 (51.6)	0.676
Race			0.292
Caucasian	0 (0)	3 (9.7)	
African American	2 (28.6)	18 (58.1)	
Hispanic	4 (57.1)	8 (25.8)	
Other	1 (14.3)	2 (6.4)	
Height (inches)	64.3±2.4	66.6±3.9	0.138
BMI (kg/m ²)	39.2±9.5	33.9±5.6	0.190
Smoking Status			0.585
Nonsmoker	5 (71.4)	18 (57.6)	
Current Smoker	0 (0)	4 (12.9)	
Former Smoker	2 (28.6)	9 (29.0)	
HTN	4 (57.1)	22 (71.0)	0.656
DM	4 (57.1)	13 (41.9)	0.678
CKD	1 (14.3)	4 (12.9)	1.000
CAD	2 (28.6)	3 (9.7)	0.223
CHF	0 (0)	9 (27.9)	0.164
ESRD	0 (0)	1 (3.2)	1.000
Asthma	0 (0)	5 (16.1)	0.561
<i><u>Follow Up</u></i>			
Days after Hosp	74.4±41.8	74.9±34.5	0.997
mMRC dyspnea score	0.86±0.90	1.40±1.13	0.246
6MWD (feet)	984±206	960±249	0.834
FEV ₁ (%predicted)	88.4±13.3	84.7±19.9	0.644
FVC (%predicted)	88.0±15.2	85.2±19.2	0.724
FEV ₁ /FVC	79.7±6.9	77.8±6.9	0.522
TLC (%predicted)	80.3±15.0	81.1±15.1	0.534
DLCO (%predicted)	89.9±12.6	55.5±12.2	<0.0001
DLCO/VA (%predicted)	111.7±13.1	82.6±17.4	<0.0001

Definition of Abbreviations: DLCO = diffusing capacity of carbon monoxide; BMI = body mass index; HTN = hypertension; DM = diabetes mellitus; CKD = chronic kidney disease; CAD = coronary artery disease; CHF = congestive heart failure; ESRD = end stage renal disease; mMRC = modified Medical Research Council; 6MWD = 6-minute walk distance; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; TLC = total lung capacity; DLCO/VA = DLCO adjusted for alveolar volume

Table 2. Group Characteristics of Hospitalization.

	Normal DLCO n=7	Low DLCO n=31	p
<u><i>Labs</i></u>			
Admission Hgb (g/dL)	13.6±0.99	12.87±1.63	0.292
Peak Ferritin (ng/mL)	247±190	656±751	0.138
Peak CRP (mg/dL)	8.4±6.5	7.1±5.0	0.597
Peak LDH (U/L)	242±58	348±149	0.075
Peak D-dimer (ng/mL)	538±208	4676±10417	0.268
Peak Fibrinogen (mg/dL)	646±173	486±189	0.267
<u><i>Medical Therapies</i></u>			
Corticosteroids	1 (14.3)	12 (38.7)	0.115
Remdesivir	1 (14.3)	7 (22.6)	0.255
Anakinra	0 (0)	1 (3.2)	0.451
IVIG	0 (0)	1 (3.2)	0.451
Tocilizumab	0 (0)	4 (12.9)	0.327
<u><i>CT Measures</i></u>			
BV5 (mL)	79.9±39.9	81.0±39.2	0.943
BV5_10 (mL)	42.6±6.9	54.2±13.3	0.005
BV10 (mL)	93.0±33.4	138.1±53.1	0.001
Opacification (mL)	89.8±90.8	221.7±272.3	0.218
<u><i>Hospital Characteristics</i></u>			
LOS (days)	4.43±1.51	6.26±5.96	0.429
Peak O2 Req (L/min)	0.57±0.98	5.66±12.55	0.433
Room Air	5 (71.4)	17 (54.8)	
NC O2	2 (28.6)	8 (25.8)	
HFNC O2	0 (0)	4 (12.9)	0.650
IMV	0 (0)	2 (6.5)	
New PE	0 (0)	2 (6.5)	1.000
New DVT	0 (0)	1 (3.2)	1.000

Definition of Abbreviations: DLCO = diffusing capacity of carbon monoxide; Hgb = hemoglobin; CRP = C-reactive protein; LDH = lactose dehydrogenase; IVIG = intravenous immunoglobulin; LOS = length of stay; NC = nasal cannula; HFNC = high flow nasal cannula; IMV = invasive mechanical ventilation; PE = pulmonary embolism; DVT = deep venous thrombosis

Figures

Figure 1

CONSORT Diagram.

Figure 2

Pulmonary vascular volumes of 2 COVID-19 patients on hospital admission. The patient in Panel A had a DLCO of 117% predicted at follow-up. The patient in Panel B had a DLCO of 32% predicted at follow-up. Blood vessels are colored according to their size. Red denotes the small vessels (5 mm), yellow the mid-size vessels (5-10 mm), and blue the larger vessels (>10 mm).

Figure 3

Pulmonary vascular volumes of pulmonary vessels $< 5\text{mm}^2$. HC = Healthy Controls.

Figure 4

Pulmonary vascular volumes by DLCO groups. A) BV5_10 and B) BV10. HC = Healthy Controls.

Figure 5

Correlation between BV10 and DLCO.