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Research paper

COVID-19 and the effects on pulmonary function following infection: A retrospective analysis

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ABSTRACT

Background: The coronavirus disease 2019 (COVID-19) has been identified in over 110 million people with no studies comparing pre-infection pulmonary function to post-infection. This study's aim was to compare pre-infection and post-infection pulmonary function tests (PFT) in COVID-19 infected patients to better delineate between preexisting abnormalities and effects of the virus.

Methods: This was a retrospective multi-center cohort study. Patients were identified based on having COVID-19 and a pre- and post-infection PFT within one year of infection during the time period of March 1, 2020 to November 10, 2020.

Findings: There was a total of 80 patients, with an even split in gender; the majority were white ($n = 70$, 87·5%) and never smokers ($n = 42$, 52·5%). The majority had mild to moderate COVID-19 disease ($n = 60$, 75·1%) with 25 (31·2%) requiring hospitalization. There was no difference between the pre- and post-PFT data, specifically with the forced vital capacity (FVC) ($p = 0·52$), forced expiratory volume in 1 s (FEV1) ($p = 0·96$), FEV1/FVC($p = 0·66$), total lung capacity (TLC) ($p = 0·21$), and diffusion capacity (DLCO)($p = 0·88$). There was no difference in the PFT when analyzed by hospitalization and disease severity. After adjusting for potential confounders, interstitial lung disease (ILD) was independently associated with a decreased FEV1 (-2·6 [95% CI, -6·7 to - 1·6] vs. -10·3 [95% CI, -17·7 to -2·9]; $p = 0·03$) and an increasing age ($p = 0·01$) and cystic fibrosis (-1·1 [95% CI, -4·5 to- 2·4] vs. -36·5 [95% CI, -52·1 to -21·0]; $p < 0·01$) were associated with decreasing FVC when comparing pre and post infection PFT. Only increasing age was independently associated with a reduction in TLC ($p = 0·01$) and DLCO ($p = 0·02$) before and after infection.

Interpretation: This study showed that there is no difference in pulmonary function as measured by PFT before and after COVID-19 infection in non-critically ill classified patients. There could be a relationship with certain underlying lung diseases (interstitial lung disease and cystic fibrosis) and decreased lung function following infection. This information should aid clinicians in their interpretation of pulmonary function tests obtained following COVID-19 infection.

Funding: No funding was obtained for this study.

1. Introduction

As of mid-February 2021, the coronavirus disease 2019 (COVID-19) has been identified in 192 countries/regions world-wide with over 110 million known cases and over 2.4 million global deaths [1]. Many patients have recovered from the initial illness but have had significant morbidity for many months following the infection with ongoing symptoms including fatigue, insomnia, muscle weakness, and dyspnea [2]. Of greater concern is long term lung damage caused by infection with COVID-19 [3]. There is currently little known about the post-infectious long-term complications from the severe acute respiratory syndrome coronavirus two (SARS-CoV-2) with much extrapolated from severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS) pandemics during 2003 and 2012, respectively [4,5]. The extrapolated data has shown that there are long-term reductions in pulmonary function, as measured by pulmonary function testing (PFT), most significantly for diffusion capacity for carbon monoxide (DLCO) for up to two years after infection [5–9]. Studies on SARS-CoV-2 have recently described pulmonary function derangements in the early convalescent period after COVID-19 infection [10,11]. One study of 57 patients previously infected showed a similar pattern of decreased pulmonary function as measured by diffusion capacity at 30 day follow up, in 75% of the

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Research in context

Evidence before this study

We searched PubMed for studies that followed patients who were infected with COVID-19 and looked at post-infection respiratory complications up to 2/10/2021, without any language exclusion. The search terms used were (COVID-19 OR SARS-CoV-2 OR Coronavirus) AND (follow up OR long term) AND (pulmonary function OR respiratory). The studies found from this search all reported that patients with COVID-19 all had changes in their pulmonary function for the worse after their infection. However, none of these studies had comparative data of these patients prior to the infection. The true change in pulmonary function after COVID-19 infection remains unknown.

Added value of this study

To our knowledge, this is the first study to compare pre-COVID 19 infection pulmonary function tests to post-COVID-19 infection pulmonary function tests. Our findings show that, there is no change in pulmonary function tests in patients who had a COVID-19 infection at about three months after infection. In multivariate analysis, patients with interstitial lung disease, cystic fibrosis, and increasing age have decreases in their lung function following infection.

Implication of all the available evidence

At three months after infection, pulmonary function was worse in patients with interstitial lung disease, cystic fibrosis, and with increasing age, which should allow for specific targeting for long-term interventions to help with recovery.

studied patients [10]. Another study on pulmonary function following infection with SARS-CoV-2, showed consistent results with decreased DLCO in 25% of 55 patients at three months following infection [11].

These previous studies have evaluated lung function following an infection of broad severities, and with unknown pre-infection baseline pulmonary function. This study aimed to compare pre-infection and post-infection pulmonary function tests (PFT) in COVID-19 infected patients.

2. Methods

2.1. Participants and study design

This was a retrospective multi-center cohort study using patient data from one tertiary referral healthcare institution located in three different US regions (Midwest, Southeast, and Southwest) with a combined bed capacity of 2631 inpatient beds (2059 beds in the Midwest, 304 beds in the Southeast, and 268 in the southwest). Patients were identified based on SARS-CoV-2 infection positivity from March first, 2020 to November tenth, 2020. The Institutional Review Board approved this study (#20−004,983). Patient informed consent was not required as information was obtained using chart review.

Patients were initially identified as having a PFT and testing positive for COVID-19 by an electronic medical record search. To be included, those identified patients had to have a PFT within one year before and following their COVID-19 diagnosis date. The date of COVID-19 diagnosis was based on the first positive polymerase chain reaction test for SARS-CoV-2. In patients with more than one before and after PFT, the one closest to the date of infection was used for pre-PFT, and the farthest from infection was used as post-PFT. Patients were excluded if they were younger than 18 years old, and if they elected to be excluded from research. The included patient population with post infection PFT were primarily obtained through post-COVID-19 infection follow-up not as part of a COVID-19 long haulers clinic.

2.2. Data collection

The electronic medical record was used to extract clinical data on demographics, comorbidities, laboratory results (to help determine comorbidities), chest imaging (chest CT scans and x-rays), COVID-19 specific therapies, hospitalization if necessary, and outcomes. Comorbidities included in the search included obesity (BMI $\geq$ 30), chronic obstructive pulmonary disease, asthma, interstitial lung disease (idiopathic pulmonary fibrosis, nonspecific interstitial pneumonias, hypersensitivity pneumonitis, connective tissue related interstitial lung disease, and other idiopathic interstitial pneumonias), bronchiectasis, bronchiolitis, cystic fibrosis, alpha-1 antitrypsin deficiency, history of lung transplant, pulmonary hypertension, obstructive sleep apnea (OSA), systolic and diastolic heart failure, arrhythmias, systemic hypertension, diabetes mellitus type 1 and 2, hematologic malignancy, solid organ malignancy, on immunosuppressant medications, chronic kidney disease stage 3 or worse, liver cirrhosis, human immunodeficiency virus positive, and history of venous thromboembolism. For analysis, comorbidity data was grouped into organ specific diseases (pulmonary, cardiac, transplant, immunosuppressed, kidney, liver, and venous thromboembolism). Patient severity classification of their COVID-19 infection was based on the WHO classification [12]. Briefly, mild disease had a diagnosis of COVID-19, but with no hypoxia or evidence of viral pneumonia; moderate disease had clinical signs of pneumonia but had an oxygen saturation greater than 90% on room air; severe disease had signs of pneumonia with tachypnea greater than 30 breaths per minute, severe respiratory distress or an oxygen saturation less than 90% on room air; and critical disease had acute respiratory distress syndrome, sepsis, or septic shock.

2.3. Pulmonary function testing

All three centers participating in this study used the same equipment, quality checks, and protocols. Master screen^{TM} PFT (Vyaire Medical; Chicago, IL), total lung capacity (TLC) was obtained in the Master screen^{TM}TM Body Plethysmograph (Vyaire Medical; Chicago, IL) and test quality was determined by the ATS-ERS guidelines [13]. The forced vital capacity, forced expiratory volume at one second, FEV1/FVC ratio, TLC, and DLCO were measured during complete PFT [14]. PFT data was collected as a percent predicted based on previously published reference equations [15-18]. FEV1/FVC was reported as the raw number ratio. Interpretation of the values obtained was based on the ATS-ERS criteria [13]. The difference between the PFT values was determined and used in the analysis. All PFT data obtained will be displayed a percent predicted and not raw values.

2.4. Polymerase chain reaction testing for SARS-CoV-2

All patients in this study had diagnostic nasopharyngeal COVID-19 tests using polymerase chain reaction using either the Becton, Dickinson and Company (BD) Veritor System or the Jiangsu Rongye Technical company testing materials.

2.5. Statistical analysis

The statistical analysis plan was determined *a priori* with normality of the pulmonary function test data determined by visual inspection of histograms and using a Shapiro-Wilk test. By using these methods, the data was determined to be normal in distribution.

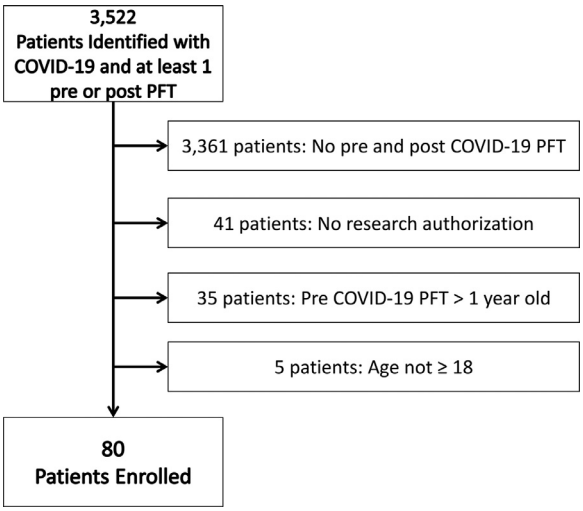

Fig. 1. Showing patient selection and exclusion criteria.

Continuous data were reported as mean (standard deviation) and categorical data were reported as frequency (percentage). A paired samples *t*-test was used for univariate analysis and, if necessary, a one-way ANOVA was used for multiple comparisons (such as race or ethnicity). For the continuous data, a linear regression model was used, which resulted in the correlation coefficient (r). Univariate analysis was performed on the pre-determined variables and difference in PFT variables. Multivariate logistic regression was performed by using all variables on univariate analysis that had a p-value less than or equal to 0·2, along with age, gender, race, ethnicity, and smoking status. Sequential analysis was performed by removing variables if they were the least significant and this was done until all variables had a p value less than 0·1. All analyses were performed using JMP® version 14·1·0 (SAS Institute Inc.; Cary, NC). Patients with missing data were not used in that specific analysis that included that data and no data was created to minimize missing data. Statistical significance was determined to be a p value less than 0·05.

2.6. Role of funding

No funding was provided for this study.

3. Results

3.1. Patient characteristics

The final cohort included a total of 80 patients (Fig. 1). Patient demographics and comorbidities are shown in Table 1. There was an even split in gender (female; *n* = 40, 50%); the majority were white (*n* = 70, 87·5%) and never smokers (*n* = 42, 52·5%). Many of these patients had lung disease (*n* = 61, 76·3%) with asthma and COPD accounting for 53 patients (66·3%). The most common non-pulmonary comorbidities included systemic hypertension (*n* = 38, 47·5%), chronic kidney disease (*n*=ten, 12·5%), and hematologic malignancy (*n* = ten, 12·5%). The most common ABO blood type was type A (*n* = 20, 51·3%).

The majority of the patients had mild to moderate COVID-19 disease (*n* = 60, 75·1%) with 25 subjects (31·2%) requiring hospitalization (Table 2). The mean hospital length of stay was 9·2 2 ± 7·1 days. Of the admitted patients, only four (five percent) required admission to the intensive care unit with one patient requiring intubation and extracorporeal membrane oxygenation. The most used COVID-19 therapies were corticosteroids (*n* = 26, 32·5%), remdesivir (*n* = 18, 22·5%), and convalescent plasma (*n* = 11, 13·8%) (Table 2).

Table 1
Baseline patient characteristics.

Variable	Data (*n* = 80)
Age at diagnosis, yrs	59.2 2 ± ± 15.0
Gender, female	40 (50.0%)
Race	
Black or African American	6 (7.6%)
American Indian	1 (1.3%)
White	70 (87.5%)
Asian	2 (2.5%)
Other	1 (1.3%)
BMI (kg/m^2)	30.7 7 ± 7.5
Obese (BMI ≥ 30 kg/m^2)	31 (38.8%)
Ethnicity, Not Hispanic	75 (93.8%)
Smoking Status	
Current	3 (3.8%)
Former	35 (43.8%)
Never	42 (52.5%)
Pre COVID-19 oxygen requirement	10 (12.7%)
Comorbidities	
COPD	24 (30.0%)
Asthma	29 (36.3%)
Interstitial lung disease	16 (20.0%)
Bronchiectasis	4 (5.0%)
Lung transplant	10 (12.5%)
Bronchiolitis	4 (5.0%)
Obstructive sleep apnea	25 (31.3%)
Heart failure	7 (8.8%)
Taking immunosuppression	13 (16.3%)
Malignancy	16 (20.0%)
Chronic kidney disease	10 (12.5%)
Liver Disease	2 (2.5%)
Venus thromboembolism	6 (7.6%)
Pulmonary embolism	5 (6.3%)
Systemic hypertension	38 (47.5%)
Cystic fibrosis	2 (2.5%)
Blood Type	
AB	3 (3.8%)
A	20 (25.0%)
B	2 (2.5%)
O	14 (17.5%)
Not available	39 (48.8%)

Categorical variables displayed as frequency (percentage). Continuous variables displayed as mean ± SD. BMI= Body mass index. COPD=Chronic obstructive lung disease.

3.2. Pulmonary function test characteristics

Pre- and post-COVID-19 infection spirometry was completed in 79 (98·8%) patients, as one patient only completed a pre-COVID-19 DLCO measurement. Pre-COVID-19 infection, 40 (50·0%) and 49 (61·3%) patients completed the TLC and DLCO portions, respectively. Post-COVID-19 infection, 38 (47·5%) and 50 (62·5%) patients completed the TLC and DLCO portions, respectively. From the date of the patient's COVID-19 diagnosis, pre-PFT were performed 148·0 0 ± 106·3 days prior and post-PFT were performed 76·9 9 ± 40·9 days after, with a time between tests of 224·9 9 ± 106·8 days.

At baseline, there were many patients that had below the lower limit of normal for the FEV1 (*n* = 40, 50·6%; 95% CI, 39·8%–61·4%), FVC (*n* = 23, 29·1%; 95% CI, 20·3%–39·9%), FEV1/FVC (*n* = 24, 30·4%; 95% CI, 21·3%–41·2%), TLC (*n* = 10, 25·0%; 95% CI, 14·2%–40·2%), and DLCO (*n* = 30, 61·2%; 95% CI, 47·2%–73·6%).

There was no difference between the pre- and post-PFT data, specifically with the FVC (82·2% % ± ± 21·3% vs. 79·9% ± 21·5%; *p* = 0·52), FEV1 (73·2% ± 22·0% vs. 73·0% ± 22·1%; *p* = 0·96), FEV1/

Table 2
COVID-19 infection related characteristics.

Variable	Data (n = 80)
COVID-19 Severity	
Mild	39 (48·8%)
Moderate	21 (26·3%)
Severe	16 (20·0%)
Critical	4 (5·0%)
Hospitalized	25 (31·3%)
Hospital length of stay, days	9·2 2 ± ± 7·1
Duration of positive nasal swab, days	59·7 7 ± ± 41·5
Intensive care unit admission	4 (5·0%)
Respiratory Support	
Nasal Cannula	16 (20·0%)
BiPAP	2 (2·5%)
High Flow	3 (3·8%)
Intubation	1 (1·3%)
Nitric Oxide	1 (3%)
COVID-19 Specific treatment	
Remdesivir	18 (22·5%)
Hydroxychloroquine	2 (2·5%)
Azithromycin	6 (7·5%)
Lenzilumab	3 (3·8%)
Tocilizumab	1 (13%)
Corticosteroids	26 (32·3%)
Convalescent Plasma	11 (13·8%)

Categorical variables displayed as frequency (percentage). Continuous variables displayed as mean ± standard deviation. BiPAP=bilevel positive airway pressure.

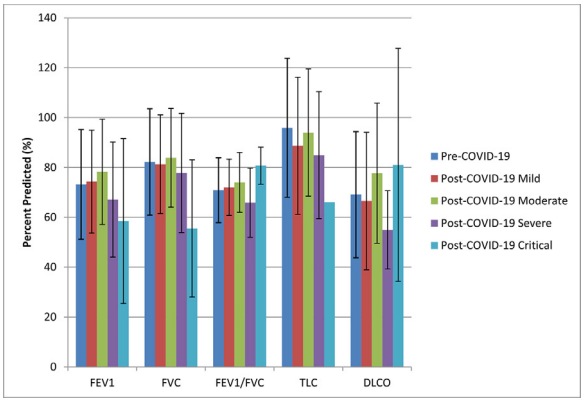

Fig. 2. Pulmonary function pre- and post-COVID-19 infection separated by infection severity

Figure showing pulmonary function test parameters before and after COVID-19 infection separated out by infection severity. The pre-COVID-19 group has all patients included pre-infection. Data is displayed as the percent predicted based off established equations with the mean and standard deviation. There were no significant differences by analysis with a paired samples t-test. FEV1=forced expiratory volume in one second; FVC=forced vital capacity; TLC=total lung capacity; DLCO=diffusion capacity for carbon monoxide. Error bars represent standard deviation. P vales as follows: FEV1 p = 0.61, FVC p = 0.59, FEV1/FVC p = 0.57, TLC p = 0.04, DLCO p = 0.053.

FVC (70·9 9 ± 13·0 vs. 71·8 8 ± 12·2; p = 0·66), TLC (95·9% ± 27·9% vs. 88·1% ± 25·9%; p = 0·21), and DLCO (69·1% ± 25·3% vs. 68·3% ± 26·9%; p = 0·88) (Fig. 2).

3.3. PFT and disease severity

The patient's requiring hospitalization had no difference in their pre- and post-COVID-19 PFT, specifically with the FVC (81·0% ± 24·7% vs. 76·5% ± 22·7%; p = 0·51), FEV1 (70·1% ± 24·1% vs. 68·5% ± 23·2%; p = 0·81), FEV1/FVC (67·9 9 ± 12·8 vs. 69·2 2 ± 13·2; p = 0·72), TLC (95·8% ± 17·3% vs. 86·4% ± 23·1%; p = 0·26), and DLCO (67·3% ± 26·2% vs. 61·0% ± 24·6%; p = 0·51) (Fig. 3). Based on COVID-19 disease

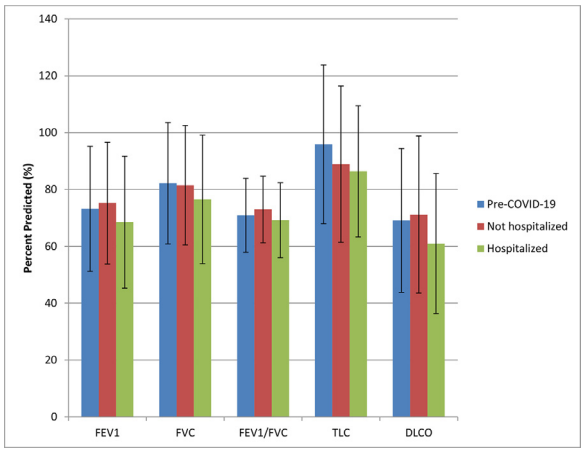

Fig. 3. Pulmonary function pre- and post-COVID-19 infection separated by need for hospitalization

Figure showing pulmonary function test parameters before and after COVID-19 infection separated out by whether the patient required hospitalization. The pre-COVID-19 group has all patients included pre-infection. Data is displayed as the percent predicted based off established equations with the mean and standard deviation. There were no significant differences by analysis with a paired samples t-test. FEV1=-forced expiratory volume in one second; FVC=forced vital capacity; TLC=total lung capacity; DLCO=diffusion capacity for carbon monoxide. Error bars represent standard deviation. P values as follows: FEV1 p = 0.81, FVC p = 0.51, FEV1/FVC p = 0.72, TLC p = 0.26, DLCO p = 0.51.

severity, there was no significant difference in the FVC% (p = 0·59), FEV1% (p = 0·61), FEV1/FVC (p = 0·57), and DLCO% (p = 0·053). The TLC % had a significantly worse change with higher disease severity (mild, −2·2 2 ± 8·9; moderate, −21·2 2 ± 24·2; severe, −12·3 3 ± 13·5; p = 0·04) (Fig. 4). COVID-19 disease severity was broken into mild, moderate and severe based on abnormal imaging, intensive care unit admission, required oxygen, and/or intubation. There was no significant difference in any of the PFT parameters, but this analysis was limited as zero patients were intubated and one patient who was admitted to the ICU had completed the TLC and DLCO tests (Table 3).

3.4. PFT and comorbidities

When the PFT change was analyzed by comorbidities, the FEV1% was decreased in patients with interstitial lung disease (0·3 3 ± 10·8 vs −6·6 6 ± 17·7; p = 0·049), and cystic fibrosis (0·8 8 ± 10·6 vs −27·0 0 ± 33·9; p < 0·01). Patients with cystic fibrosis also had decreased FVC% values (−1·5 5 ± 9·6 vs. −28·5 5 ± 30·4; p <0 ·01), while interstitial lung disease also decreased the FEV1/FVC value (1·2 2 ± 5·6 vs. −4·9 9 ± 20·4; p = 0·04). Age had significant impacts on the TLC% (r = −0·48; p = 0.01) and DLCO% (r = −0·41; p=<0·01). When all the lung diseases were grouped together, this showed a decrease in the DLCO% (6·2 2 ± 15·3 vs. −5·2 2 ± 15·4; p = 0·046) (Supplemental Table one).

3.5. Multivariate analysis

After adjusting for potential confounders, interstitial lung disease was independently associated with a decreased FEV1 (−2·6 [95% CI, −6·7 – −1·6] vs. −10·3 [95% CI, −17·7 to −2·9]; p = 0·03). Both an increasing age (p = 0·01) and cystic fibrosis (−1·1 [95% CI, −4·5 – −2·4] vs. −36·5 [95% CI, −52·1 to −21·0]; p < 0·01) were associated with decreasing FVC. Only increasing age was independently associated with a reduction in TLC (p = 0·01) and DLCO (p = 0·02). See table 4 for full list of variables used in multivariate analysis.

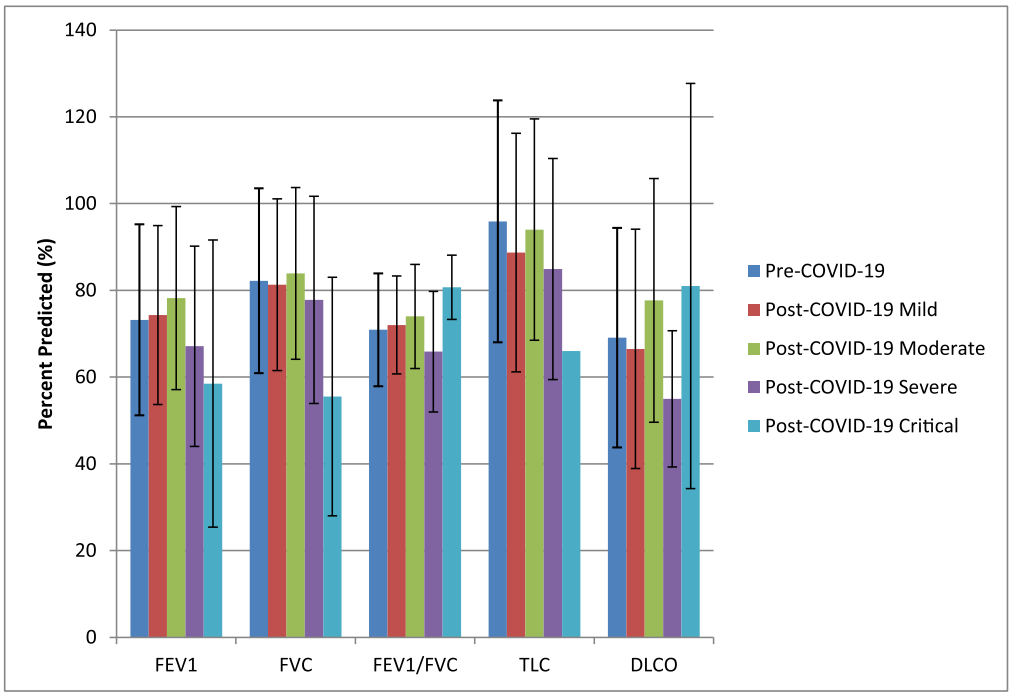

Fig. 4. Pulmonary function pre- and post-COVID-19 infection separated by infection severity

Figure showing pulmonary function test parameters before and after COVID-19 infection separated out by infection severity. The pre-COVID-19 group has all patients included pre-infection. Data is displayed as the percent predicted based off established equations with the mean and standard deviation. There were no significant differences by analysis with a paired samples *t*-test. FEV1=forced expiratory volume in one second; FVC=forced vital capacity; TLC=total lung capacity; DLCO=diffusion capacity for carbon monoxide. Error bars represent standard deviation.

4. Discussion

The current trajectory of patients recovering from the novel COVID-19 virus is not yet known, but this is the first study, to our knowledge, to show that there was no change in pulmonary function at three to four months post-COVID-19 infection when compared to pre-infection PFT among those with mild to moderate disease. The majority of the patients in this study were not hospitalized and very few had critical illness. This study includes predominantly those with milder disease severity, which among the general population is the common severity of disease. Older patients with interstitial lung disease as well as cystic fibrosis had decreased pulmonary function parameters following infection. In contrast patients who underwent hospitalization, had abnormal chest imaging, and required oxygen after infection all had no significant differences in their pulmonary function tests during the same timeframe.

It was noted that patients with interstitial lung disease were more likely to have decreased lung function on their PFT. The ILD category included all patients with diffuse parenchymal lung diseases (including idiopathic, connective tissue disease associated, smoking related diseases, respiratory bronchiolitis, cryptogenic organizing pneumonia, and acute interstitial lung disease). This could be related to increased fibroblastic activation in ILD, similar to what was seen in a paper studying lung infections and their progression to ARDS with poor effects on lung function [19]. In less severe ILD cases without ARDS, viral infection has been associated with fibrosis initiation, progression, reduced lung function, and even exacerbation. Also, patients with cystic fibrosis showed a decline in their lung function following infection, which has been seen in other viral illnesses, such as influenza [20,21]. The data regarding cystic fibrosis was obtained by only having two patients, making this less reliable. In comparison to the influenza A, H1N1, pandemic of 2009 where there was an increased risk of death and long term symptoms that we also see with COVID-19, the H1N1 pandemic showing increased rates of long term pulmonary limitations (including decreased DLCO and increased small airway disease [22,23]).

These results are contradictory to previous studies regarding PFT following COVID-19 infection; however, prior studies were not able to compare pre-COVID-19 PFT to post-COVID-19 PFT [24–26]. This study is the first to evaluate post COVID-19 PFT using the same patients and pre-COVID-19 PFT as the baseline. Two of these three previously referenced studies included about half the number of patients as this study. Also, as described in this current study, many of the patients had abnormal PFT values even before their COVID-19 infection. This raises the question of whether prior studies were describing changes due to COVID-19 infection, or whether they were sampling a patient population with existing underlying lung disease that left them susceptible to significant COVID-19 infection.

By measuring PFT before and after infection with COVID-19, in non-critically ill classified patients, this has allowed us to better delineate if the abnormalities seen on pulmonary function are due to pre-existing disease or sequelae of COVID-19. Other studies have performed PFT up to four months out from infection, but again the prior studies did not compare to PFT before infection [27]. This study provides insight on prognosis for patients with disease manifestations that were mild enough to be treated at home or in the hospital without the use of intubation (only 3·2% of infected patients require intubation) or positive pressure ventilation [28]. Most patients who were diagnosed with COVID-19 within our study patient population had a benign clinical course, mirroring the CDC estimates of only 452·2 out of 100,000 patients diagnosed with COVID-19 are severe enough to be hospitalized [29]. Overall, this data suggests a return to baseline pulmonary function in most patients diagnosed with COVID-19.

A study evaluating computed tomography findings in patients recovering from COVID-19 infection showed that those who progressed to fibrotic changes were more likely to have an increased age and higher severity of illness [30]. This is consistent with the presented data that lung function is likely to return to baseline in this study's sample, which consisted mainly of patients that did not

Table 3

	FEV1	FVC	FEV1/FVC	TLC	DLCO
Smoking History	$p = 0.37$	$p = 0.85$	$p = 0.28$	$p = 0.87$	$p = 0.24$
Current	2.3 (−12.2−16.9)	−3.7 (−19−11.7)	5.3 (−9.4−20)	–	0 (−32−32)
Former	0.9 (−1.6−5.1)	−2.2 (−6.7−2.3)	1.7 (−1.8−5.2)	−8.8 (−17.9−0.3)	−6.6 (−13.5−0.18)
Never	−3 (−6.9−0.9)	−4 (−8−0.14)	−1.7 (−5−- 1.5)	−9.8 (−19.7−0- 0)	1.8 (−5.4−8.9)
Prior use of O_2	0.6 (−7.5−8.7) $p = 0.67$	0.3 (−8.1−8.7) $p = 0.39$	−0.7 (−7.4−6.1) $p = 0.85$	−9.5 (−23.5−4.5) $p = 0.95$	−1.9 (−14.4−10.7) $P = 0.9$
Obesity	−0.5 (−5.0−4.1) $p = 0.72$	−1.4 (−6.1−3.3) $p = 0.34$	−2.8 (−6.5−1.0) $p = 0.07$	−1.0 (−13.2−11.2) $p = 0.12$	0.8 (−8.1−9.8) $p = 0.36$
Medical history of:					
Lung disease	−0.8 (−4−2.4) $p = 0.72$	−3 (−6.4−0.4) $p = 0.81$	−0.45 (−3.2−2.3) $p = 0.54$	−8.6 (−16- −1.2) $p = 0.68$	−5.2 (−10.7−0.18) $p = 0.05$
COPD	1.%2 (−4.1−6.2) $p = 0.32$	−3 (−8.4−2.4) $p = 0.92$	2 (−2.4−6.4) $p = 0.27$	−10 (−20.4−0.07) $p = 0.81$	−7.8 (−15.5−0.18) $p = 0.08$
Asthma	0.9 (−3.8−5.6) $p = 0.3$	−2.2 (−7.1−2.7) $p = 0.63$	1.%2 (−2.7−5.1) $p = 0.42$	−11.7 (−25.5−2.2) $p = 0.69$	−1.7 (−12.1−8.6) $p = 0.85$
ILD	−6.6 (−12.8−0.4) $p = 0.049$	−7 (−13.5−0.5) $p = 0.2$	−4.9 (−10−0.3) $p = 0.04$	−8.3 (−20.3−3.8) $p = 0.84$	−3.6 (−13.1−5.8) $p = 0.8$
Bronchiectasis	1.75 (−10.9−14.4) $p = 0.65$	1.5 (−11.7−14.7) $p = 0.47$	0.2 (−10.4−10.7) $p = 0.97$	–	–
Lung transplant	−3.6 (−11.6−4.4) $p = 0.51$	−3 (−11.4−5.4) $p = 0.96$	−1.5 (−8.2−5.2) $p = 0.64$	2(−15.9−21.9) $p = 0.17$	−1.3 (−20.2−17.5) $p = 0.89$
Bronchiolitis	8.3 (−4.2−20.7) $p = 0.13$	9.5 (−3.4−22.4) $p = 0.05$	−0.7 (−11.2- 9.9) $p = 0.9$	0.33 (−18.9−19.6) $p = 0.28$	−3 (−21.9−15.9) $p = 0.96$
OSA	−2.1 (−7.1−3) $p = 0.64$	−3.4 (−8.7−1.8) $p = 0.91$	0.04 (−4.2−4.3) $p = 0.96$	−15.6 (−25.8−5.4) $p = 0.12$	−2.6 (−11−5.8) $p = 0.99$
Heart failure	−4.9 (−14.4−4.7) $p = 0$ 0.41	−6.6 (−16.5−3.4) $p = 0.48$	0.23 (−8.4−8.9) $p = 0.95$	−11.5 (−35.6−12.6) $p = 0.84$	−6.3 (−25.2−12.5) $p = 0.68$
Arrhythmia	−9.9 (−19.2−0.5) $P = 0.05$	−9.7 (−19.6−0.15) $p = 0.17$	−1.4 (−10−7.2) $p = 0.74$	−26 (−59.3−7.3) $p = 0.3$	−6.5 (−29.6−16.6) $p = 0.73$
Immunosuppression	2.6 (−4.4−9.6) $P = 0.25$	0.6 (−6.7−7.9) $p = 0.26$	0.8 (−5−6.7) $p = 0.75$	−2.3 (−14.7−10.1) $p = 0.19$	1.%2 (−8.9−11.5) $p = 0.39$
Heme malignancy	1.%2 (−6.8−9.2) $P = 0.54$	−0.2 (−8.5−7.1) $p = 0.45$	1.%2 (−6.5−6.8) $p = 0.95$	−5.5 (−19.3−8.3) $p = 0.53$	−1.4 (−13−10.2) $p = 0.81$
Solid malignancy	0.67 (−9.8−11) $p = 0.73$	−8.8 (−19.5−1.9) $P = 0.28$	7 (−1.4−15.5) $p = 0.09$	−23 (−46−0.3) $p = 0.22$	−12.4 (−26.7−1.8) $P = 0.15$
Diabetes	−7.2 (−17.4- 3.1) $p = 0.22$	−6.8 (−17.6−3.9) $p = 0.48$	−1.1 (−9.7−7.5) $p = 0.8$	−0.5 (−24.3−23.3) $p = 0.44$	0 (−18.9−18.9) $p = 0.78$
CKD	−7.2 (−15.1−0.67) $p = 0.10$	−6.6 (−14.9−1.7) $p = 0.39$	−1.6 (−8.7−5.4) $P = 0.63$	3.7 (−15.1−22.5) $p = 0.14$	−1.5 (−17.9−14.8) $P = 0.89$
Liver cirrhosis	5.5 (−12.4−23.4) $P = 0.46$	3.5 (−15.1−22.1) $p = 0.47$	2.9 (−12−17.8) $p = 0.7$	2(−30.7−36.7) $P = 0.45$	−1 (−24.1−22.1) $p = 0.89$
VTE	−7.8 (−18−2.4) $p = 0.18$	−8.2 (−18.9−2.6) $p = 0.34$	−3.3 (−12.7−6.1) $p = 0.5$	−11.5 (−35.6−12.6) $p = 0.84$	−11 (−34−12) $p = 0.45$
Pulmonary HTN	0 (−25.3−25.3) $P = 0.93$	0 (−26.4−26.4) $p = 0.81$	0.4 (−20.7−21.5) $p = 0.97$	2(−30.7−36.7) $p = 0.45$	−2 (−34.7−30.7) $p = 0.97$
Pulmonary embolism	−7 (−18.3−4.2) $P = 0.28$	−9 (−20.7−2.7) $p = 0.31$	2(−7.5−11.4) $p = 0.66$	−8.5 (−25.5−8.5) $p = 0.92$	−7.25 (−23.5−9) $P = 0.55$
Systemic HTN	−3.8 (−7.8−0.23) $P = 0.07$	−5.7 (−9.9−1.5) $p = 0.11$	−1.2 (−4.7−2.2) $p = 0.35$	−13 (−21.6−4.7) $p = 0.16$	−2.7 (−10.2−4.8) $p = 0.96$
Cystic Fibrosis	−27 (−44.1−9.9) $p < 0.01$	−28.5 (−44−13) $p < 0.01$	−0.2 (−8.3−7.9) $p = 0.85$	–	–
Alpha 1 antitrypsin	5.5 (−12.4- −23.4) $p = 0.46$	4.5 (−14−23) $p = 0.41$	0.4 (−14.6−15.3) $p = 0.96$	1 (−30.7−36.7) $p = 0.45$	4(−29.7−35.7) $p = 0.73$

Table showing mean difference between pre- and post-infection pulmonary function tests. Data is displayed as mean (95% confidence interval). Data is displayed as mean (95% confidence interval). FEV1= forced expiratory volume in 1 second, FVC= forced vital capacity, TLC= total lung capacity, DLCO= diffusion capacity for carbon monoxide. Heme=hematologic, CKD=chronic kidney disease, HIV= human immunodeficiency virus, VTE= Venus thromboembolism, HTN= hypertension,.

Table 4
Multivariate analysis covariates.

FEV1	FVC	TLC	DLCO
Age	Age	Age	Age
Gender	Gender	Gender	Gender
Race	Race	Race	Race
Ethnicity	Ethnicity	Ethnicity	Ethnicity
Smoking status	Smoking status	Smoking status	Smoking status
Interstitial lung disease	Interstitial lung disease	Oxygen requirement	ICU admission
Bronchiolitis	Bronchiolitis	COVID severity	Oxygen requirement
Arrhythmia	Arrhythmia	Systemic hypertension	Lung disease
Chronic kidney disease	Systemic hypertension	Chronic kidney disease	COPD
VTE	Cystic fibrosis	On immunosuppression	Solid organ malignancy
Systemic hypertension		Obstructive sleep apnea	
Cystic fibrosis		History of lung transplant	
		Obesity	

FEV1= forced expiratory volume in 1 second. FVC= forced vital capacity. TLC= total lung capacity. DLCO= diffusion capacity. VTE= venus thromboembolism. ICU= intensive care unit. COPD= chronic obstructive pulmonary disease.

require invasive mechanical ventilation. There have been several expert opinion papers that have looked at severe disease in the younger population and what could be causing this [31,32]. Our study does not have a large population in the 18−34-year-old age group, but we do see variation in outcomes with increasing age and this would be an excellent area for additional research.

It is possible that the decreases seen in DLCO in prior studies were present prior to infection but were not yet known. It is likely that there are some changes to the PFT values that are seen during active infection and the early convalescent period that resolve with time and would explain why studies with shorter follow-up intervals are noting decreased function [10,11].

Other studies have attempted to look at the various treatments received for COVID-19 infection and their effect on lung function after convalescence [2,3,10]. There has not yet been much published on this to date. Currently the recommended treatments for COVID-19 are changing rapidly, leading to small numbers of patients that received a given therapy in our patient population, which was too small to analyze. In addition, at the time of this publication, there are no current therapies regularly recommended for non-hospitalized patients. Whether therapeutic interventions have an impact of long-term lung function in more severe illness would be an area for future research.

Limitations to our study include the retrospective design of this study. Given the novel SARS-CoV-2 virus, there was no opportunity to design a prospective study given the need for PFT before this virus was declared a world-wide pandemic. The statistical analysis of TLC and DLCO measurements was limited by the small sample size, with only being about half of the cohort size, but is still larger than any other studies evaluating PFT after infection with COVID-19. Our patient cohort consisted predominately of female and non-Hispanic white subjects, given the retrospective nature, there was no way to improve this limitation. We acknowledge the effect this may have on the ability to generalize our findings on a more demographically diverse population, but we were unable to control for this given the observational nature of the study. Another limitation is that there was a small number of critically ill patients included this study, which precluded an effective analysis. Many of those patients did not survive making post-infection PFT unobtainable. As time goes on, the number of patients with pre- and post-COVID-19 PFT will increase and will provide more robust numbers for analysis.

This study included mild and moderate disease with 20% of patients being severe or critical disease. Based on the small numbers of critically ill patients, a trend towards worsening lung function, there is likely a component of lung fibrosis and destruction of alveoli causing reduced PFT values. Autopsies performed on patients after COVID-19 infection have shown varying degrees of interstitial fibrosis which is identical to ARDS [33,34]. There may even be a component of myopathy from COVID-19 causing diaphragm weakness and decreased PFT values in severe and critically ill patients [35]. This study suggests that the pulmonary function tests of patients that recover from COVID-19, without the use of intubation or positive pressure ventilation, are likely to return to pre-infection values.

4.1. Data sharing

The data that support the findings of this study are available from the corresponding author upon reasonable request.

5. Author contribution

Kristyn L Lewis is the guarantor for this manuscript, with Kristyn L Lewis, Scott A Helgeson, and Mehmet M Tatari having verified the underlying data. All authors (Kristyn L Lewis, Scott A Helgeson, Mehmet M Tatari, Jorge M Mallea, Hassan Z Baig, and Neal M Patel) contributed substantially to the study idea, study design, data analysis and interpretation, and writing and editing the manuscript. All authors (Kristyn L Lewis, Scott A Helgeson, Mehmet M Tatari, Jorge M Mallea, Hassan Z Baig, and Neal M Patel) approved this final version of the manuscript and agree to be accountable for all aspects of this work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of Competing Interest

We declare no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2021.101079.

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