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Original Research

## Differences in lung function between major race/ethnicity groups following hospitalization with COVID-19

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## A B S T R A C T

**Background:** Ethnic minorities have higher rates of infection, hospitalization, and death from COVID-19 compared to White Americans.**Research question:** Is race/ethnicity an independent predictor of lung dysfunction following hospitalization with COVID-19?**Study design:** and **Methods:** Patients hospitalized at the University of Virginia Medical Center with COVID-19 underwent a questionnaire within 30 days following discharge. Those who had persistent respiratory symptoms were invited to complete spirometry, lung volumes, and diffusion capacity of carbon monoxide. 128 completed pulmonary function testing at 6 months.**Results:** Impairments in lung function were present in spirometry, lung volumes, and diffusion capacity of carbon monoxide at 6 months. The most prevalent impairments were noted in FVC (24.4%), FEV1 (20.5%), TLC (23.3%), and DLCO (20.8%). When compared between race/ethnicity groups three lung function parameters demonstrated statistically significant difference, including FEV1/FVC ( $p = 0.021$ ), RV/TLC ( $p = 0.006$ ) and DLCO % predicted ( $p = 0.002$ ). The average difference between Hispanic and non-Hispanic Black patients with respect to DLCO % predicted was 13.09 ( $p = 0.01$ ) and the average difference between non-Hispanic White and non-Hispanic Black patients was 9.46 ( $p = 0.04$ ). Differences persisted when controlling for age, BMI, smoking status, history of chronic lung disease, ICU admission, treatment with corticosteroids, and socioeconomic status.**Interpretation:** Long-term impairments in lung function following COVID-19 are common, occurring in roughly 22% of patients and across all three major domains of lung function. Non-Hispanic Black race/ethnicity was associated with a statistically significant lower DLCO % predicted when compared to non-Hispanic White and Hispanic patients.

## 1. Introduction

A significant percentage of patients infected with the novel coronavirus (COVID-19) report debilitating symptoms months following infection. A community-based study from the United Kingdom of half-a-million individuals found that 38% reported one of two major clusters of symptoms categorized as either “tiredness” or “respiratory” at 12 weeks post-infection [1].

In addition to subjective symptoms, multiple studies have demonstrated objective findings of lung dysfunction following COVID-19. Studies have varied widely with respect to population size, time to follow up, and COVID-19 severity, however, the majority have demonstrated lung function abnormalities with prevalence ranging from 25 to 50% [2–5]. The most consistently documented and long-lasting abnormalities have been decreases in diffusion capacity of carbon dioxide (DLCO) and total lung capacity (TLC) [2,3,6–8].

Risk factors for developing objective lung dysfunction following COVID-19 remain somewhat poorly characterized. Similar to severe adult respiratory syndrome (SARS) and middle eastern respiratory syndrome (MERS) the most consistent findings suggest a correlation with the severity of illness and the need for mechanical ventilation [4,5,9].

One factor which has unfortunately been missing from the reported data is the impact of COVID-19 on lung function compared across varied racial/ethnic groups. This is particularly relevant in the United States where COVID-19 has disproportionately affected minority populations. Early in the pandemic, limited epidemiologic data found that African Americans were dying at a disturbing four times the rate of White Americans [10]. Subsequent larger database studies have corroborated that ethnic minorities, including Hispanics, African Americans, Native Americans, and Asian Americans had substantially higher rates of infection, hospitalizations, and death compared to White Americans [11]. Data looking at long-term pulmonary dysfunction have been

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### Abbreviations

|          |                                                                   |
|----------|-------------------------------------------------------------------|
| AC       | anticoagulation                                                   |
| ADI      | area deprivation index                                            |
| CCI      | Charleston Comorbidity index                                      |
| CRP      | c-reactive protein                                                |
| ECMO     | extracorporeal membrane oxygenation                               |
| IQR      | interquartile range                                               |
| LLN      | lower limit of normal                                             |
| MERS     | middle eastern respiratory syndrome                               |
| NIH      | National Institute of Health                                      |
| NH Black | non-Hispanic Black                                                |
| NH White | non-Hispanic White                                                |
| P/F      | partial pressure of arterial oxygen to fractional inspired oxygen |
| RRT      | renal replacement therapy                                         |
| SARS     | severe adult respiratory syndrome                                 |
| UVA      | University of Virginia                                            |
| VTE      | venothromboembolism                                               |
| WHO      | World Health Organization                                         |

almost entirely limited to people of Asian or European descent and in the vast majority of studies coming out of China or Italy, ethnicity is not commented on at all [2–4,9,12,13].

This study sought to identify and characterize functional pulmonary outcomes 6 months following infection with SARS-CoV-2 in a racially/ethnically diverse population that more accurately represented the United States population. Additionally, we sought to further clarify potential risk factors for prolonged respiratory impairment in an attempt to provide physicians and patients with more robust prognostication skills.

## 2. Material and methods

### 2.1. Case Definition and Patient Selection

We performed a single-center, prospective cohort study of adults with COVID-19 hospitalized at the University of Virginia Medical Center (UVA) with polymerase chain reaction (PCR) confirmed SARS-CoV-2 infection between the months of March 2020 and January 2021. The indications for hospitalization were guided strongly by recommendations from the National Institute of Health and included the following: an oxygen saturation of <94% on room air, respiratory rate >30 breaths per minute, PaO<sub>2</sub>/FiO<sub>2</sub> < 300 mmHg, or lung infiltrates >50%. Within 30 days of discharge, patients received a phone call in which they were asked a 10-point symptom-based questionnaire (Fig. 1). Two Spanish-speaking physicians were utilized to assist in the completion of questionnaires amongst Spanish-only speaking individuals. Those who answered “YES” to questions 1–8 were invited to follow up for pulmonary function testing (PFT); including spirometry, lung volumes, and diffusion capacity of carbon monoxide (DLCO).

Patients who agreed to participate were offered a referral to UVA’s post-COVID clinic at three- and six-months post hospital discharge in which they underwent a standardized intake process that included assessments of pulmonary symptom burden, psychological symptom burden,<sup>1</sup> pulmonary function testing and offered future follow up as needed or requested. Before clinic encounters patients underwent financial screening and were provided with sliding scale financial assistance based on need. Inclusion and exclusion criteria are

summarized in Table 3. The study design was reviewed and approved by the Institutional Review Board of Health Science Research at the University of Virginia (IRB-HSR # 23182).

### 2.2. Pulmonary function testing

All patients underwent standard pulmonary function testing (PFT) including spirometry, lung volumes, and DLCO. Total lung capacity was determined by the single-breath CO technique. The hemoglobin value was evaluated before PFT to apply the appropriate correction to DLCO. The spirometer underwent calibration the day the test was performed, and barometric pressure and temperature were simultaneously recorded. A trained technician coached the patient, while a pulmonologist (A. K, C.R) was responsible for test validation and interpretation based on the 2005 American Thoracic Society and European Respiratory Society statements [14].

### 2.3. Outcomes

Measured outcomes included the following: percent predicted of forced vital capacity (FVC % pred), percent predicted of forced expiratory volume in the 1st second (FEV1% pred), the ratio of forced expiratory volume in the 1st second to forced vital capacity (FEV1/FVC), percent predicted of total lung capacity (TLC % pred), percent predicted of residual volume (RV % pred), the ratio of residual volume to total lung capacity (RV/TLC), and the percent predicted of diffusion capacity of carbon monoxide (DLCO % pred). PFT variables with values less than the lower limit of normal (<LLN) were considered abnormal. In patients with prior PFT data who had baseline values of <LLN a decrease in the percent predicted of >5% was considered abnormal.

### 2.4. Evaluation of socioeconomic status

The Area Deprivation Index (ADI) is a method of ranking neighborhoods by socioeconomic status. It is based on a measure created by the Health Resources and Services Administration and adapted by researchers at the University of Wisconsin, Madison [15]. It includes domains of income, education, employment, and housing quality. The national percentile ranges from 1 to 100 with 100 representing the most disadvantaged. The state decile ranges from 1 to 10 with 10 representing the most disadvantaged.

### 2.5. Statistical analysis

The above lung function variables were compared across three major race/ethnicity subgroups, (1) Hispanic, (2) Non-Hispanic Black (NH Black), and (3) Non-Hispanic White (NH White) to assess for a potential effect of race/ethnicity on lung function outcomes. Significant differences between groups were identified by p-values <0.05. Lung function variables that had p-values <0.05 were compared using Turkey’s post-hoc test in order to identify pair-wise differences.

Multivariable linear regression analysis was performed with respect to DLCO % predicted. This outcome variable was chosen because there was a statistically significant difference between race/ethnicity groups and because previous studies have shown it to be one of the most commonly affected pulmonary function variables affected by COVID-19 infection. Variables included in the analysis were race/ethnicity, age, BMI, smoking status, history of chronic lung disease (self-reported asthma, COPD, or ILD), ICU admission, treatment with corticosteroids, and socioeconomic status as measured by the area deprivation index (ADI). Certain variables that differed between race/ethnicity groups were excluded from analysis due to strong collinearity. This included the Charleston co-morbidity index which correlated with age as well as the need for intubation, admission P/F ratio and severity scales which all correlated strongly with ICU admission. Categorical variables were recorded as counts and percentages, normal continuous variables with

<sup>1</sup> The following psychometric questionnaires were used: PROMIS depression, MOCA, Neuro-Quality of life, and Insomnia Severity Index.

1. If you were discharged on supplemental oxygen, are you still requiring it?
2. Are you continuing to require inhalers? If you used inhalers before, are you using them more frequently than prior to your hospitalization?
3. Do you have a persistent cough?
4. Do you feel your health is still negatively affected by COVID-19?
5. Have you been unable to return to work due to fatigue or breathlessness?
6. Do you have new or worse shortness of breath? At rest, with activity, or both?
7. Do you tire easily with routine day to day activity?
8. Do you have new and persistent muscle weakness or fatigue?
9. Do you smoke?
10. Did you have underlying lung disease prior to your hospitalization?

Fig. 1. 30-day discharge questionnaire.

mean and standard deviation, and non-normal continuous with median and IQR.

### 3. Results

#### 3.1. Study population

Between March 2020 and January 2021, 234 consecutive patients hospitalized with PCR positive SARS-CoV-2 received a 30-day post-discharge screening phone call, of which 128 completed pulmonary function testing at 6 months (average time to follow up 186 days). The selection process and associated attrition are illustrated in Fig. 2. The main characteristics of participants are included in Table 1 and Table 2.

Out of the 128 who completed pulmonary function testing the median age was 54 years ( $\pm 14$ ) of whom 43% were female. The majority were never smokers although 38% had chronic lung disease either in the form of self-reported asthma, COPD, or idiopathic pulmonary fibrosis.

Of those patients, only 10% had previously available PFTs to corroborate their diagnosis and compare changes. The most common comorbidities were type II diabetes (50%), self-reported asthma (25%), and COPD (13%). The average Charleston Comorbidity Index score was 2.7. The Area Deprivation Index (ADI) was similar across all the major race/ethnicity groups with an average state decile value of 6.2 (IQR 5–8).

With regards to treatment and severity, the majority of patients received corticosteroid, remdesivir, or both. Over 90% of the patients were characterized as either severe or critical by the World Health Organization (WHO) ordinal severity scale with 70% of the population requiring admission to the ICU.

The racial/ethnic diversity of the patient population was robust and included 35% Hispanic, 28% NH Black, and 32% NH White, however, fell short in recruiting patients from Asian backgrounds which represented only 4% of the population.

When compared across race/ethnicity groups several baseline characteristics were found to be statistically different, including age,

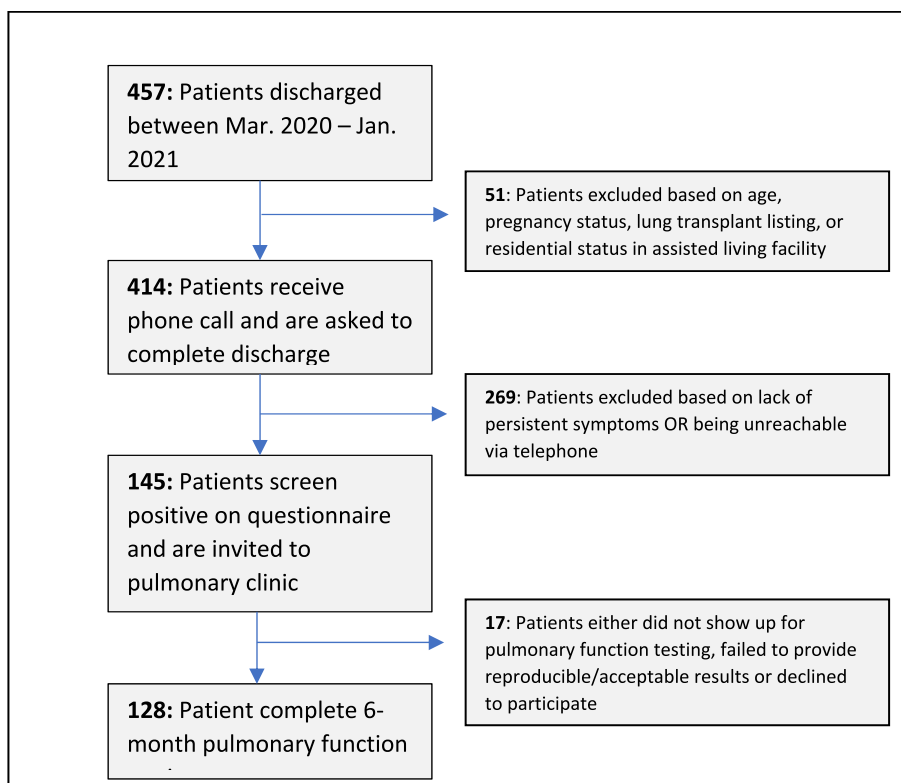


Fig. 2. Patient selection and attrition.

**Table 1**  
Demographics, comorbidities, and treatments in the study population compared across race/ethnicity.

| Demographics                               | Hispanic (n = 45) | Non-Hispanic Black (n = 36) | Non-Hispanic White (n = 41) | Total Population (n = 128) | p-value |
|--------------------------------------------|-------------------|-----------------------------|-----------------------------|----------------------------|---------|
| Age, y (SD)                                | 47 (±12)          | 57 (±16)                    | 57 (±12)                    | 54 (±14)                   | <.01    |
| Gender, female (%)                         | 16 (36)           | 19 (53)                     | 19 (46)                     | 56 (43)                    | 0.27    |
| Smoking status                             |                   |                             |                             |                            | 0.016   |
| Never                                      | 33 (73)           | 15 (42)                     | 20 (49)                     | 70 (55)                    |         |
| Former                                     | 11 (24)           | 17 (47)                     | 20 (49)                     | 51 (39)                    |         |
| Current                                    | 1 (2)             | 4 (11)                      | 1 (2)                       | 7 (5)                      |         |
| Socioeconomic Status, median (IQR)         |                   |                             |                             |                            |         |
| ADI (state decile)                         | 5.8 (4–8)         | 6.2 (4.5–8)                 | 6.8 (6–8)                   | 6.2 (5–8)                  | 0.25    |
| ADI (national percentage)                  | 43.2 (32–62)      | 47.3 (32.5–63)              | 53.5 (44.2–65.2)            | 47 (35–62)                 | 0.28    |
| Comorbidities                              |                   |                             |                             |                            |         |
| BMI, median (IQR), kg/m <sup>2</sup>       | 35.4 (29.9–40.1)  | 40.1 (31.8–45.7)            | 33.2 (26.4–37.8)            | 35.81 (29.54–40.51)        | 0.01    |
| Idiopathic Pulmonary Fibrosis              | 1 (2)             | 1 (3)                       | 0 (0)                       | 2 (1)                      | 0.59    |
| Asthma (self-reported)                     | 5 (11)            | 15 (42)                     | 14 (34)                     | 32 (25)                    | <.01    |
| COPD                                       | 0 (0)             | 5 (14)                      | 4 (10)                      | 10 (13)                    | 0.08    |
| Myocardial Infarction                      | 0 (0)             | 2 (5)                       | 3 (7)                       | 6 (5)                      | 0.2     |
| Cerebrovascular Disease                    | 0 (0)             | 4 (11)                      | 3 (7)                       | 8 (6)                      | 0.09    |
| Heart Failure                              | 1 (2)             | 6 (17)                      | 3 (7)                       | 11 (9)                     | 0.06    |
| Chronic Liver Disease                      | 2 (4)             | 1 (3)                       | 2 (5)                       | 5 (4)                      | 0.89    |
| Moderate to Severe CKD                     | 0 (0)             | 1 (3)                       | 1 (2)                       | 3 (2)                      | 0.54    |
| Cancer                                     | 2 (4)             | 3 (8)                       | 2 (5)                       | 9 (7)                      | 0.72    |
| Immune Suppression/HIV                     | 2 (4)             | 1 (3)                       | 0 (0)                       | 9 (7)                      | 0.31    |
| Type II Diabetes                           | 24 (53)           | 17 (47)                     | 20 (49)                     | 64 (50)                    | 0.85    |
| Charleston Comorbidity Index, median (IQR) | 1.84 (0.5–3)      | 3.39 (1.25–5)               | 2.95 (1.5–4)                | 2.7 (1–4)                  | <.01    |
| Treatments Associated with COVID-19        |                   |                             |                             |                            |         |
| Corticosteroids                            | 20 (44)           | 17 (47)                     | 30 (73)                     | 72 (56)                    | 0.02    |
| Remdesivir                                 | 16 (36)           | 13 (36)                     | 28 (68)                     | 59 (46)                    | 0.02    |
| Tocilizumab                                | 4 (9)             | 0 (0)                       | 4 (10)                      | 8 (6)                      | 0.16    |
| Hydroxychloroquine                         | 4 (9)             | 3 (8)                       | 2 (5)                       | 9 (7)                      | 0.75    |
| Convalescent plasma                        | 7 (16)            | 5 (14)                      | 10 (24)                     | 23 (18)                    | 0.42    |

IQR = interquartile range; ADI = area deprivation index; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease; HIV = human immunodeficiency virus. Values are n (%), or median (interquartile range).

**Table 2**  
Markers of disease severity and markers of inflammation of the study group compared across race/ethnicity.

| Disease Severity                      | Hispanic (n = 45) | Non-Hispanic Black (n = 36) | Non-Hispanic White (n = 41) | Total Population (n = 128) | p-value |
|---------------------------------------|-------------------|-----------------------------|-----------------------------|----------------------------|---------|
| Admission P/F (SD)                    | 224 (±119)        | 318 (±147)                  | 246 (±119)                  | 260 (±133)                 | <0.01   |
| Admission to ICU (%)                  | 38 (84)           | 19 (53)                     | 27 (66)                     | 90 (70)                    | <.01    |
| Need for Intubation                   | 30 (67)           | 13 (36)                     | 16 (39)                     | 64 (50)                    | <.01    |
| Need for vasopressors                 | 23 (51)           | 10 (28)                     | 11 (27)                     | 48 (38)                    | 0.03    |
| Need for RRT                          | 1 (2)             | 1 (3)                       | 3 (7)                       | 5 (4)                      | 0.45    |
| Need for ECMO                         | 3 (7)             | 1 (3)                       | 0 (0)                       | 4 (3)                      | 0.29    |
| Evidence of VTE                       | 4 (9)             | 2 (6)                       | 6 (15)                      | 12 (9)                     | 0.4     |
| Need for oxygen at discharge, LPM     | 9 (20)            | 10 (28)                     | 12 (29)                     | 30 (23)                    | 0.66    |
| New AC start                          | 11 (24)           | 8 (22)                      | 13 (32)                     | 33 (26)                    | 0.6     |
| WHO ordinal scale (0–8)               |                   |                             |                             |                            | 0.01    |
| 3                                     | 2 (4)             | 5 (14)                      | 4 (10)                      | 11 (9)                     |         |
| 4                                     | 9 (20)            | 15 (41)                     | 17 (41)                     | 41 (32)                    |         |
| 5                                     | 4 (9)             | 2 (6)                       | 4 (10)                      | 11 (9)                     |         |
| 6                                     | 8 (18)            | 4 (11)                      | 4 (10)                      | 17 (13)                    |         |
| 7                                     | 22 (49)           | 10 (28)                     | 12 (29)                     | 48 (36)                    |         |
| Median WHO ordinal scale (IQR)        | 5.86 (5–7)        | 4.97 (4–7)                  | 5.07 (4–7)                  | 5.39 (4–7)                 | 0.01    |
| NIH severity scale                    |                   |                             |                             |                            | 0.027   |
| Moderate                              | 2 (4)             | 5 (14)                      | 4 (10)                      | 11 (9)                     |         |
| Severe                                | 8 (18)            | 15 (42)                     | 16 (39)                     | 39 (30)                    |         |
| Critical                              | 35 (78)           | 16 (44)                     | 21 (51)                     | 78 (61)                    |         |
| Markers of Inflammation, median (IQR) |                   |                             |                             |                            |         |
| Highest D-dimer (ng/mL)               | 938 (431–3013)    | 639 (265–2460)              | 622 (297–2019)              | 754 (351–2462)             | 0.55    |
| Highest CRP (mg/dL)                   | 14.5 (6.2–23.9)   | 9.2 (3–20.1)                | 11.2 (7.5–13.9)             | 12.6 (4.25–19.1)           | 0.22    |
| Highest ferritin (ng/mL)              | 1066 (342–2260)   | 522 (203–1263)              | 580 (198–1348)              | 686 (257–1557)             | 0.16    |

ICU = intensive care units; RRT = renal replacement therapy; ECMO = extracorporeal membrane oxygenation; VTE = venothromboembolism; LMP = liters per minute; AC = anticoagulation; WHO = World Health Organization; NIH = National Institute of Health; CRP = c-reactive protein. Values are n (%), mean (interquartile range), median (interquartile range).

smoking status, body mass index, Charleston co-morbidity index, self-reported asthma, treatment allocation, admission to the ICU, need for intubation, and disease severity. Compared to NH Black and NH White patients respectively, Hispanic patients were more likely to be younger (mean age 47 vs 57 vs 57), never smokers (73% vs 42% vs 49%), and have more severe disease as measured by the WHO ordinal scale, NIH severity scale and need for ICU admissions (78% vs 44% vs 51%).

Finally, Hispanic and NH Black patients were less likely to receive corticosteroids or remdesivir than NH White patients despite no obvious indication that they would have lacked the appropriate indications.

### 3.2. Evaluation of pulmonary sequelae

Impairments in lung function (as defined by values < LLN) were

**Table 3**  
Inclusion and exclusion criteria.

| Inclusion Criteria: |                                                                                           |
|---------------------|-------------------------------------------------------------------------------------------|
| •                   | Age between 18 and 85                                                                     |
| •                   | Diagnosis of SARS-CoV-2 infection by positive PCR on nasal-pharyngeal swab                |
| •                   | Hospitalized due to COVID-19                                                              |
| Exclusion Criteria: |                                                                                           |
| •                   | Cognitive dysfunction precluding the ability to participate in pulmonary function testing |
| •                   | Currently undergoing work up for lung transplant                                          |
| •                   | Currently resident in a long-term care facility <sup>a</sup>                              |
| •                   | Pregnant                                                                                  |

<sup>a</sup> Patients residing at long term care facilities were excluded by the study investigators due to the perceived difficulties of transportation, successful completion of acceptable/reproducible PFTs and the ability to provide informed consent.

present across all three domains including spirometry, lung volumes, and DLCO at 6 months. The most prevalent impairments were noted in FVC (24.4%), FEV1 (20.5%), TLC (23.3%), and DLCO (20.8%). The least

**Table 4**  
Spirometry, lung volumes and diffusion capacity of carbon monoxide compared across race/ethnicity subgroups.

|                           | Hispanic<br>(n = 45) | Non-<br>Hispanic<br>Black (n =<br>36) | Non-<br>Hispanic<br>White (n =<br>41) | Total<br>(n =<br>128) | p-<br>value |
|---------------------------|----------------------|---------------------------------------|---------------------------------------|-----------------------|-------------|
| <b>Spirometry</b>         |                      |                                       |                                       |                       |             |
| FVC %                     | 85.63 ±              | 85.24 ±                               | 85.56 ±                               | 85.98                 | 0.995       |
| predicted                 | 17.68                | 14.85                                 | 19.28                                 | ± 17.49               |             |
| (mean ±                   |                      |                                       |                                       |                       |             |
| sd)                       |                      |                                       |                                       |                       |             |
| FVC < LLN                 | 13 (28.9)            | 6 (17.1)                              | 12 (29.3)                             | 31                    | 0.395       |
|                           |                      |                                       |                                       | (24.4)                |             |
| FEV1%                     | 89.07 ±              | 83.09 ±                               | 87.59 ±                               | 87.09                 | 0.396       |
| predicted                 | 17.80                | 19.93                                 | 20.54                                 | ± 19.16               |             |
| (mean ±                   |                      |                                       |                                       |                       |             |
| sd)                       |                      |                                       |                                       |                       |             |
| FEV1 < LLN                | 7 (15.6)             | 8 (22.9)                              | 11 (26.8)                             | 26                    | 0.434       |
|                           |                      |                                       |                                       | (20.5)                |             |
| FEV1/FVC1                 | 83.71 ±              | 76.62 ±                               | 80.76 ±                               | 80.46                 | 0.021       |
| (mean ±                   | 7.80                 | 15.44                                 | 8.67                                  | ± 11.13               |             |
| sd)                       |                      |                                       |                                       |                       |             |
| FEV1/FVC1                 | 2 (4.4)              | 6 (17.1)                              | 2 (4.9)                               | 10 (7.9)              | 0.077       |
| < LLN                     |                      |                                       |                                       |                       |             |
| <b>Lung Volumes</b>       |                      |                                       |                                       |                       |             |
| TLC %                     | 85.32 ±              | 81.83 ±                               | 81.44 ±                               | 83.32                 | 0.465       |
| predicted                 | 13.92                | 14.60                                 | 15.16                                 | ± 14.44               |             |
| (mean ±                   |                      |                                       |                                       |                       |             |
| sd)                       |                      |                                       |                                       |                       |             |
| TLC < LLN                 | 6 (13.6)             | 10 (30.3)                             | 12 (32.4)                             | 28                    | 0.097       |
|                           |                      |                                       |                                       | (23.3)                |             |
| RV %                      | 85.81 ±              | 94.53 ±                               | 82.44 ±                               | 87.54                 | 0.16        |
| predicted                 | 22.03                | 34.98                                 | 19.95                                 | ± 26.27               |             |
| (mean ±                   |                      |                                       |                                       |                       |             |
| sd)                       |                      |                                       |                                       |                       |             |
| RV < LLN                  | 7 (15.9)             | 3 (9.1)                               | 5 (13.5)                              | 15                    | 0.679       |
|                           |                      |                                       |                                       | (12.5)                |             |
| RV/TLC                    | 31.54 ±              | 39.23 ±                               | 35.50 ±                               | 35.19                 | 0.006       |
| (mean ±                   | 10.48                | 9.66                                  | 8.50                                  | ± 9.86                |             |
| sd)                       |                      |                                       |                                       |                       |             |
| RV/TLC <                  | 4 (9.1)              | 2 (6.1)                               | 3 (8.1)                               | 10 (8.3)              | 0.886       |
| LLN                       |                      |                                       |                                       |                       |             |
| <b>Diffusion Capacity</b> |                      |                                       |                                       |                       |             |
| DLCO %                    | 97.05 ±              | 80.55 ±                               | 83.62 ±                               | 87.35                 | 0.002       |
| predicted                 | 19.76                | 23.21                                 | 20.08                                 | ± 21.97               |             |
| (mean ±                   |                      |                                       |                                       |                       |             |
| sd)                       |                      |                                       |                                       |                       |             |
| DLCO < LLN                | 6 (13.3)             | 9 (26.5)                              | 11 (27.5)                             | 26                    | 0.214       |
|                           |                      |                                       |                                       | (20.8)                |             |

Forced vital capacity = FVC; lower limited of normal = LLN; forced expiratory volume in the 1st second (FEV1); total lung capacity (TLC); residual volume (RV); diffusion capacity of carbon monoxide (DLCO).

prevalent impairments were seen in FEV1/FVC (7.9%), RV (12.5%), and RV/TLC (8.3%) (Table 4).

When compared between race/ethnicity groups three lung function parameters demonstrated statistically significant difference, including FEV1/FVC ( $p = 0.021$ ), RV/TLC ( $p = 0.006$ ) and DLCO % predicted ( $p = 0.002$ ). No differences, however, were seen in the incidence of impairment (values < LLN) of any lung function parameter between race/ethnicity groups.

The mean FEV1/FVC was 83.71 in Hispanic patients, 76.62 in NH Black, and 80.76 in NH White ( $p = 0.021$ ). Turkey's test for comparison of means confirmed that differences in FEV1/FVC were isolated to Hispanic vs NH Black while no differences were seen in other pair-wise comparisons. The mean RV/TLC was 31.34 in Hispanic patients, 39.93 in NH Black, and 35.50 in NH White ( $p = 0.006$ ). Again, differences were isolated to Hispanic vs. NH Black. Finally, the mean DLCO % predicted was 97.1% in Hispanic patients, 80.1% in Non-Hispanic Black, and 83.6% in Non-Hispanic White ( $p = 0.002$ ). Only in DLCO % predicted were differences present between more than one pair-wise comparison. Hispanic patients had a higher mean DLCO % predicted (97.1%) when compared to both NH Black (80.6%) and NH White (83.6%).

Given that we saw statistically significant differences between race/ethnicity groups in FEV1/FVC and RV/TLC (both utilized in understanding obstructive lung disease) we performed a dual variable linear regression comparing the effect of race/ethnicity and a history of COPD or asthma on these variables. We found that a history of COPD and/or asthma was 16 x more powerful at predicting FEV1/FVC than race/ethnicity and 4 x more powerful with respect to RV/TLC than race/ethnicity, suggesting that the observed difference was more likely due to the presence of more COPD and/or asthma in the NH Black cohort.

Multivariable analysis was performed with respect to DLCO % predicted. While taking into account a patient's age, BMI, smoking status, history of chronic lung disease (self-reported asthma, history of COPD or ILD), need for ICU admission, treatment with corticosteroids, and area deprivation index, the race/ethnicity of a patient still maintained a significant association with the percent predicted of DLCO. Holding these other variables constant, the average difference between Black and Hispanic patients was 13.09 ( $p = 0.01$ ) and the average difference between Black and White patients was 9.46 ( $p = 0.04$ ). (Table 5). Multivariable analysis also demonstrated that age, BMI, history of chronic lung disease and ADI all had statistically significant effects on DLCO % predicted.

#### 4. Discussion

To our knowledge, this is the first attempt to assess lung function outcomes following COVID-19 specifically with respect to race/ethnicity in a diverse patient population. Multivariable linear regression demonstrated that race/ethnicity had a statistically significant association with DLCO % predicted, with NH Black patients having lower DLCO

**Table 5**  
Effect of variables on DLCO percent predicted.

| Variable                                     | DLCO % change (std err) | P-value |
|----------------------------------------------|-------------------------|---------|
| Race (ref = black)                           |                         |         |
| Hispanic                                     | 13.09 (4.99)            | 0.01    |
| White                                        | 9.46 (4.53)             | 0.04    |
| Age                                          | -0.39 (0.14)            | <0.01   |
| BMI                                          | 0.79 (0.18)             | <0.001  |
| Smoking status (ref = never)                 |                         |         |
| Current                                      | -5.82 (8.11)            | 0.48    |
| Former                                       | -4.54 (3.78)            | 0.31    |
| History of chronic lung disease <sup>a</sup> | -8.30 (3.93)            | 0.04    |
| ICU admission                                | -7.48 (4.26)            | 0.08    |
| Treated with corticosteroids                 | -0.66 (3.77)            | 0.86    |
| ADI state decile                             | -2.03 (0.91)            | 0.03    |

BMI = body mass index; ICU = intensive care unit; ADI = area deprivation index.

<sup>a</sup> = self-reported asthma, COPD, or ILD. Adjusted  $R^2 = 0.38$ .



% predicted compared to Hispanic and NH White patients even when corrected for important inter-groups differences. Whether this association represents some hidden confounder or is directly related to genetic variance is unknown.

When considering a possible mechanistic cause for this association, it is worth noting the pathophysiologic role of angiotensin converting enzyme receptor 2 (ACE-2) in SARS-CoV-2 infection and the ethnic distribution of specific ACE-1 polymorphism in the United States. Firstly, ACE-2 receptors are expressed on respiratory epithelial cells and serve as the binding site for SARS-CoV-2 and subsequent entry into the cell [16]. Secondly, there are three major ACE-1 gene polymorphisms which have been identified corresponding to the deletion (D) or insertion (I) of a 287 bp sequence in intro 16, including DD homozygous, II homozygous and ID heterozygous [17]. And finally, homozygous D allele (*ACE-1 D*) is associated with greater upregulation of ACE-2 receptors and is found in a larger proportion of NH Black patients in the United States [18]. Therefore, the presence of *ACE-1 D* alleles in the NH Black population, which leads to upregulation of surface ACE-2 receptors, could conceivably result in more significant respiratory disease and subsequent dysfunction in NH Black patients in the United States.

When comparing the outcomes of the population as a whole to the available literature we encountered several obstacles. The time frame to follow up varied greatly ranging from 30 days to 1 year, the severity of illness skewed heavily towards the more mild/moderate end of the spectrum (compared to our more critical/severely ill patients), various degrees of smoking history, and chronic lung disease were included and different pulmonary function testing values were reported.

Faverio et al. [12] performed the most similar study in terms of both time to follow up (6 months) and severity (38% requiring intubation) although included a population with substantially more “never smokers” (75% vs 55%) and excluded patients with prior history of COPD. Comparing the two study populations as a whole we found less impairment in TLC % predicted (<LLN; 23% vs 46%) and DLCO % predicted (<LLN; 21% vs 46%) but found a higher degree of impairment in FEV1/FVC (<LLN; 7.9% vs 2%).

A national cohort study performed in Switzerland by Guler et al. [13] had a similar patient population with respect to severity (62% requiring intubation), had fewer “never smokers” (18% vs 55%), and included patients with a history of COPD (13% vs 13%) but assessed lung function at 4 months. Additionally, Guler et al. only reported mean percent predicted values of lung function rather than specifying the presence or absence of abnormal values. Compared to our study population patients with severe/critical disease had a significantly better mean FEV1/FVC (94.7 vs 80.4). The mean TLC % predicted was similar (86 vs 83%) and the mean DLCO % predicted was significantly worse (73% vs 86%).

#### 4.1. Strengths

The most notable strength of the study was our novel attempt to associate lung function outcomes with respect to differences in race/ethnicity. This is particularly relevant as racial/ethnic minorities have been more severely impacted by the COVID-19 pandemic [19]. Recently, Ejike et al. published a paper in The American Journal of Respiratory and Critical Care Medicine which demonstrated that differences in health outcomes for NH Black adults with COPD were only partially ameliorated after adjustment for socioeconomic factors suggesting some contribution from either hidden confounders or genetics [20]. We also attempted to address the impact of socioeconomic factors by collecting the Area Deprivation Index for each patient. In our multivariable analysis ADI was found to be an independent predictor of DLCO % predicted. With each decile increase in ADI value (representing a higher degree of deprivation) DLCO % predicted decreased by 2% ( $p = 0.03$ ) [2].

Furthermore, we made a targeted effort to recruit Hispanic members of the community by utilizing two Spanish-speaking physicians to help perform the telephone surveys (S.K. C.H.-C). We believe similar attempts

should be made in future studies when designing research protocols to help increase the contribution from normally under-represented race/ethnicity groups. Finally, recruitment was high with 58% of patients who were screened completing PFTs compared to only 44% in a comparably sized study [3].

#### 4.2. Limitations

We identified several significant limitations of the study. The first limitation was the presence of a strong selection bias. Rather than attempting to collect follow-up data on all patients hospitalized with COVID-19 we limited our efforts to those with persistent symptoms due to resource limitations within the pulmonary function laboratory. Therefore, our estimates of lung function abnormalities should only be extended to patients who remain symptomatic 30 days following discharge from the hospital. Additionally, 17 patients (12%) of those with persistent symptoms either did not show up for pulmonary function testing, failed to provide reproducible/acceptable results or declined to participate, further contributing to a significant degree of selection bias.

Second, a substantial proportion of patients had a prior diagnosis of either asthma or COPD. We attempted to correct for this by comparing prior PFTs to post-discharge PFTs but only 10% of patients had prior PFTs available. This would have skewed our data towards lower FEV1/FVC ratios and this concern was corroborated when comparing FEV1/FVC to studies of similar size, follow up time and disease severity [12, 13].

Third, we did not include in our analysis any radiographic data (either computed tomography or plain film radiography). Doing so would have allowed us to correlate changes to pulmonary function tests with structural changes to the lung. Presumably, if structural lung changes would have differed between race/ethnicity groups this could have generated more robust evidence that the differences in lung function were true findings and not due to chance or hidden confounders.

Finally, although similar in size to comparable studies, the limited number of patients impaired our ability to perform more robust linear regression which is evident by our relatively small adjusted R-squared value. Furthermore, a limited amount of abnormal values for dichotomous variables (above or below LLN) impaired our capacity to perform a risk assessment analysis such as odds ratios for specific variables. In our linear regression of comparing the effects of race/ethnicity on DLCO % predicted we excluded some baseline patient characteristics that were statistically different between the three race/ethnicity groups and would conceivably affect lung function outcomes. These included the Charleston co-morbidity index (CCI), disease severity indices, admission P/F ratios, and need for intubation. Although all of these variables demonstrated either strong collinearity with age and/or need for ICU admission and therefore were likely accounted for to some extent.

## 5. Conclusion

This single-center, prospective cohort study of lung function 6-months following hospitalization from COVID-19 demonstrated abnormalities across all three domains of lung function: spirometry, lung volumes and DLCO. The most prominent lung function abnormalities were noted in FVC (24.4%), FEV1 (20.5%), TLC (23.3%) and DLCO (20.8%). NH Black race/ethnicity was associated with a statistically significant lower DLCO % predicted when compared to NH White and Hispanic patients. Differences persisted when controlling for age, BMI, smoking status, history of chronic lung disease, ICU admission, use of corticosteroids and socioeconomic status.

#### CRedit authorship contribution statement

**Samuel B. Konkol:** Conceptualization, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. **Chintan Ramani:** Conceptualization, Investigation, Resources, Writing – review

& editing, Supervision, Project administration. **David N. Martin:** Conceptualization, Software, Validation, Formal analysis, Visualization. **Carissa K. Harnish-Cruz:** Investigation, Data curation, Writing – review & editing. **Kelsie M. Mietla:** Investigation, Data curation, Writing – review & editing. **Ryan F. Sessums:** Investigation, Data curation, Writing – review & editing. **John C. Widere:** Investigation, Data curation, Writing – review & editing. **Alexandra Kadl:** Conceptualization, Investigation, Resources, Data curation, Writing – review & editing, Supervision, Project administration, Funding acquisition.

### Declaration of competing interest

All the authors have read the manuscript and have approved it for submission to *Respiratory Medicine*. None of the authors have any conflicts of interest to disclose. The tables are original and do not require permission.

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- **Samuel B Konkol:** Author. Responsible for study design, patient questionnaires, data entry, primary manuscript author, secondary data analysis. SBK had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

- **Chintan Ramani:** Author. Responsible for study design, performance/interpretation of PFTs, contributing editor of manuscript

- **Carissa K Harnish-Cruz:** Author. Responsible for patient questionnaires, data entry, contributing editor of manuscript

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