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The clinical impact of the COVID-19 pandemic first wave on patients with cystic fibrosis in New York

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A B S T R A C T
Background: People with cystic fibrosis (pwCF) may be at risk of complications from COVID-19 but the impact of COVID-19 on pwCF remains unknown.

Methods: We conducted a multicenter retrospective cohort study to assess the impact of COVID-19 pandemic first wave on pwCF in the New York metropolitan area (NY) from March 1, 2020 to August 31, 2020.
Introduction

The New York (NY) metropolitan area was one of the hardest hit regions by the coronavirus 2019 disease (COVID-19) pandemic in the United States (U.S.), raising the question of how the pandemic affected the region’s large cystic fibrosis (CF) population. The first NY COVID-19 case was confirmed on March 1, 2020. Hospitals quickly became inundated with critically ill patients with COVID-19 acute respiratory distress syndrome (ARDS). Elective surgeries were suspended, and outpatient clinics quickly turned to telehealth care. Within 3 months, COVID-19 deaths accumulated to over 21,000 in NY, 110,000 in the U.S., and 400,000 worldwide [1]. By one year, the U.S. death toll exceeded 500,000 people [1].

Risk factors for COVID-19 hospitalization include obesity, diabetes mellitus, cardiovascular disease, chronic lung disease, and immunosuppression [2]. People with cystic fibrosis (pwCF) are predisposed to respiratory infections due to impaired mucociliary clearance resulting from genetic variants encoding for abnormal cystic fibrosis transmembrane conductance regulator (CFTR) protein. The 2009 H1N1 Influenza A pandemic saw an incidence of 2.3% to 4.4% and a 50% to 70% rate of hospitalizations in pwCF [3,4]. In contrast to the H1N1 pandemic, the COVID-19 pandemic resulted in extensive global lockdown and implementation of universal masking and contact precautions. Registry-based international studies revealed a lower-than-expected incidence of COVID-19 in pwCF from March to June 2020 compared to the general population [5–10]. First wave COVID-19 incidence in French and Italian CF centers was 0.41% and 0.40%, respectively, and lower than the general population [8–9]. The European CF Society Patient Registry reported an incidence of 0.27%, similar to the general population, however by age groups, incidence was higher in pwCF [10]. Based on the U.S. CF Foundation Patient Registry from March 1, 2020 to August 31, 2020, approximately 0.6% (196/30,000) of pwCF were COVID-19 positive, of whom 24% were hospitalized. These patients were 32% pediatric, 11% advanced CF lung disease (ACFLD) (1 death), and 4% post-lung transplant [11]. During the same period, the New York City (NYC) incidence of COVID-19 was 2.69% based on the Centers for Disease Control and Prevention and the United States Census Bureau [12–13]. COVID-19 IgG prevalence in the NYC general population within the first wave pandemic ranged from 24.3% to 44%, while at least 50% of cases were asymptomatic [14–15]. Seroprevalence in NY healthcare workers was 13.7% [16].

We conducted a multicenter retrospective cohort study to assess (1) the prevalence of COVID-19 infection in pwCF in NY, (2) the clinical characteristics, management, and outcomes of COVID-19 in pwCF, (3) the delays in routine outpatient CF care, and (4) the impact of COVID-19 on mental health for pwCF during the first wave of the pandemic. Based on observation of few COVID-19 cases within our centers and early international data, we hypothesized that the prevalence of COVID-19 would be lower in pwCF than in the NY general population. We suspected that the pandemic caused notable delay in routine outpatient care and increased anxiety and depression among pwCF.

Methods

This investigation was a multicenter retrospective cohort study including pwCF in NY from March 1, 2020 to August 31, 2020 at 12 adult and pediatric CF Centers: Northwell Health, Mount Sinai–Beth Israel, New York Medical College, New York Presbyterian–Columbia University Irving Medical Center, NYU Langone Health, and Stony Brook University Hospital. Approval was obtained from the institutional review board at each site, all of which waived the need for informed consent. Research was conducted in accordance with the Declaration of Helsinki. Data was gathered from the electronic medical record at each institution and entered into a secure REDCap (Research Electronic Data Capture) database. COVID-19 infection was diagnosed by polymerase chain reaction (PCR) or IgG antibody positivity during the study period March 1, 2020 to August 31, 2020. Testing approach and timing were based on clinical indication and patient accessibility. In-person clinic visits closed in some centers by March 13, 2020 and resumed as early as May 15, 2020 or as late as July 28, 2020; while telehealth visits were implemented. Patients suspected of COVID-19 received PCR testing. Most PCR tests were performed at urgent care centers or makeshift swabbing sites during the first wave. Antibody testing became available in NY by May 2020 and was performed before vaccination became available by December 2020, removing the possibility of immunity from vaccination. 6 of the 12 CF centers (3 pediatric and 3 adult centers) routinely offered COVID-19 antibody testing to patients while the other centers performed antibody testing on a case-by-case basis. Reasons for antibody screening included: (1) PCR testing was not readily available during the early pandemic; (2) patients did not obtain PCR testing at the time of suspected COVID-19; (3) patients exhibited symptoms indistinguishable from COVID-19; and (4) patients reported suspected exposure. Timing of antibody testing in relation to symptom onset was not controlled for as in-person clinic visits was delayed, although IgG levels may be maintained up to 7 months [17]. Antibody assays were all approved by the U.S. Food and Drug Administration (FDA) but varied across time and institutions due to supply chain shortages. One institution used 7 different assays during the study period [16]. Two such assays were the Abbot Architec SARS-CoV-2 IgG chemiluminescent microparticle immunoassay (CMIA) and the Roche Elecsys Anti-SARS-CoV-2 electro-chemiluminescence immunoassay (ECLIA). Both tests have 100% sensitivity after 14 days of infection while the specificity were 99.6% and 99.3% for
the Abbot Architect CMIA and Roche Elecsys ECLIA [18]. The Abbot Architect CMIA reported 1 false positive in a sample of 1020 specimens and the diagnostic accuracy of the Roche Elecsys ECLIA is comparable [18−19]. Consistent with prior literature in pwCF, the prevalence of COVID-19 by PCR was calculated based on the number of patients in the overall cohort [6, 8–10], as testing was often prompted by symptoms. The prevalence of COVID-19 by IgG antibody testing was calculated differently, similar to prior studies in pwCF, based on the number of patients tested [14–16], as testing was performed for screening purposes.

Examined clinical features of COVID-19 positive cases included demographic characteristics, medical comorbidities, home medications, baseline forced expiratory volume in one second (FEV1), suspected source of infection, reason for testing, symptoms, treatments received, management at home or in hospital, and mortality. Noteworthy symptoms different from baseline for the study period were recorded to define changes preceding and temporally related to the time of testing for PCR and serology-positive patients. Asymptomatic refers to the absence of unique illness symptoms patients recalled during the study period, rather than at the time of testing. As a post-hoc analysis, we also used chi-squared tests to compare the following variables between the COVID-19 positive cases in our cohort and in the remainder of the New York CF population (1075 = CF registry population (1101) minus the positive cases (26) in our cohort): F508del variant homozygous mutation status, diabetes, pancreatic insufficiency, ACFLD (defined as FEV1 < 40%), and use of any CFTR modifier, elexacaftor/tezacaftor/ivacaftor (ETI), chronic azithromycin, chronic oral corticosteroids, dornase alfa, and hypertonic saline.

Delay in care (DC) was assessed from March 1, 2020 to May 31, 2020 when most in-person visits were closed. DC was defined as a composite variable including at least one care plan that was not performed within an expected time frame and may be routine or patient-specific. DC included missed opportunities in one or more of the following: office visit, laboratory testing (which included microbiology and blood testing), pulmonary function testing, elective surgery or invasive procedure, diagnostic imaging, subspecialty follow-up, or postponement of lung transplant listing.

Patient anxiety and depression were assessed qualitatively by each CF Center’s social worker or clinician by phone or during a clinic visit. Patients were excluded if (1) the center was not able to reach patient by phone, or (2) baseline or follow-up mental health assessment were not completed during the study period. At the center level, we compared total clinical encounters, including in-person office visits and telehealth visits, and CF pulmonary exacerbations from March 1, 2020 to May 31, 2020 to the same 3-month time span in 2019. Statistical analysis using Chi-squared tests was used to compare the prevalence of anxiety and depression in pwCF before and during the COVID-19 pandemic.

**Results**

The study cohort included 810 pwCF from 12 CF centers in NY. The prevalence of COVID-19 by PCR in pwCF in the full study cohort was 1.6% (13/810). The prevalence of COVID-19 infection by IgG antibody screening was 12.2% (18 of 147 tested). There were 26 distinct COVID-19 cases, including 5 patients testing positive by both PCR and IgG antibody, 8 by COVID-19 PCR testing alone, and 13 by COVID-19 IgG antibody testing alone (Fig. 1). Most PCR positive patients were asymptomatic (8/13) while most IgG-positive patients were asymptomatic (13/18). There were 5 PCR positive asymptomatic cases, which were tested at patients’ request for unclear reasons.

The baseline characteristics of the 26 patients who tested positive for COVID-19 are shown in Table 1. Patients ranged from 5 to 61 years old, with an average age of 28 years old and a median age of 24 years old. 46% of patients were female, 85% were Caucasian, and 42% were Hispanic. and average body mass index (BMI) was 22.4 kg/m² (median 22.31). 50% had at least one F508del variant and 23% were F508del homozygous. The 2 most common medical comorbidities were pancreatic insufficiency (96%) and CF-related diabetes (38%). Average FEV1 was 2.2 L (69% of predicted). 19% of patients had ACFLD. 46% of patients were taking CFTR modulator therapy, most commonly the highly effective CFTR modulator (HMT), ETI (Trikafta®) (31%, 8/26). Amongst the 12 patients with at least one F508del variant, 5 were not taking ETI and included 1 patient post-transplant and 4 patients less than 11 years of age, for whom ETI was not yet FDA-approved at the time.

Post-hoc analysis comparing key clinical features of pwCF with and without either a positive COVID-19 PCR or IgG antibody test are compared in Table 2. Diabetes and pancreatic insufficiency were more common among patients with either a positive COVID-19 PCR or IgG antibody test than among patients who did not have a positive COVID-19 test. The proportion of patients on CFTR modulator therapy was also lower among patients who had COVID-19.

The clinical features of patients with COVID-19 infection are summarized in Table 3. While 58% of cases were asymptomatic, the most common symptoms of COVID-19 infection were cough, shortness of breath, fever, and myalgias. Most symptomatic patients (82%) were managed at home whereas 8% were hospitalized. 85% of patients did not require treatment, 12% required new supplemental oxygen, 12% received antibiotics, 8% received corticosteroids, and 4% received remdesivir. 1 death (4%) occurred in a patient post-lung transplant, and was treated with mechanical venti-

| Demographics                                      | N = 26 |
|---------------------------------------------------|--------|
| Age                                               | 28 (16)|
| Female                                            | 12 (46)|
| Caucasian                                         | 22 (85)|
| Hispanic                                          | 11 (42)|
| Smoking                                           | 1 (4)|
| Delta F508del Mutation                            | 13 (50)|
| Delta F508del Homozygous                          | 6 (23)|
| Body Mass Index                                   | 22.4 (3.5)|

| Medical Comorbidities                             |        |
|---------------------------------------------------|--------|
| Chronic Kidney Disease                            | 1 (4)|
| Cystic Fibrosis-Related Diabetes                  | 10 (38)|
| Hepatic Disease                                   | 1 (4)|
| Hyperlipidemia                                    | 0 (0)|
| Hypertension                                      | 3 (12)|
| Liver Transplant                                  | 1 (4)|
| Lung Transplant                                   | 2 (8)|
| Pancreatic Insufficiency                           | 25 (96)|
| Pulmonary Hypertension                            | 1 (4)|

| Pulmonary Function                                |        |
|---------------------------------------------------|--------|
| FEV1, liters                                      | 2.2 (1.1)|
| FEV1, %                                           | 69 (30)|
| FVC, liters                                       | 3.0 (1.3)|
| FVC/S                                            | 77 (26)|
| FEV1/FVC                                         | 0.74 (0.1)|
| Advanced CF Lung Disease (FEV1<40%)               | 5 (19)|

| Home Medications                                  |        |
|---------------------------------------------------|--------|
| CFTR Modulator                                    | 12 (46)|
| Ivcator                                           | 1 (4)|
| Lumacaftor/Ivcator                                | 2 (8)|
| Tezacaftor/Ivcator                                | 1 (4)|
| Elexacaftor/Tezacaftor/Ivcator                    | 8 (31)|
| Azithromycin (chronic)                            | 7 (27)|
| Dornase Alfa                                      | 21 (8)|
| Hypertonic Saline                                 | 16 (62)|
| Oral Corticosteroids (chronic)                    | 1 (4)|

*Data are summarized as mean (standard deviation) for continuous variables and n (%) for categorical variables.

Table 1
Baseline characteristics of patients with cystic fibrosis and positive COVID-19 Polymerase chain reaction or IgG antibody test.*
lotion, intravenous antibiotics, corticosteroids, remdesivir, and full anticoagulation. The second hospitalized patient had ACFLD and required 3 days of high-flow oxygen.

From March 1 to May 31, 2020, 89% of subjects experienced a delay in one or more areas of outpatient CF care. These included missed or delayed office visits (40%), laboratory testing (66%), pulmonary function tests (83%), imaging (72%), invasive procedures (36%), specialty visits (45%), and active transplant listing (24%) (Fig. 2). DC for invasive procedures, specialty visits, and transplant active listing were only considered in our analysis for subjects requiring these aspects of care.

The prevalence of anxiety in our cohort increased from 43% (228/529) at baseline to 58% (305/529) during the COVID-19 pandemic (P = 0.01). There was also a trend toward increased depression from 39% (190/485) at baseline to 45% (217/485) (P = 0.08). 35% (281/810) and 40% (325/810) of patients were not screened for baseline anxiety and baseline depression, respectively, due to insufficient time for most centers to perform an annual mental health screening by March 2020 as in-person visits were limited during the first wave pandemic. The 2019 National CF Patient Registry demonstrated mental health screening of 83–90% over 1 year [20].
Clinical encounters (including in-person and telehealth visits) were 17% lower during the pandemic (950 visits between March 1, 2020 to May 31, 2020) compared to the same period one year prior (1146 visits between March 1, 2019 to May 31, 2019). Of the 950 clinical encounters, 72% were telehealth visits; telehealth visits were not routinely performed in 2019. Total pulmonary exacerbations was 51% lower from March to May 2020 compared to the same months in 2019 (172 versus 349).

Discussion

The prevalence of COVID-19 by PCR in our cohort of pwCF was 1.6%, which is lower than the NY general population rate (2.69%) but higher than in many European countries during the first wave of the pandemic [6–10]. It is not surprising that our reported prevalence in pwCF was higher than other regions internationally as NY was the epicenter of the COVID-19 pandemic’s first wave in the US. The NY CF cohort antibody positivity rate of 12.2% was lower than the seroprevalence of the NY general population at the time estimated in the literature, which may have been as high as 24–44% [14–15].

Post-hoc analysis comparing patients with either a positive COVID-19 PCR or IgG antibody and the remainder of the NY CF population based on CF registry data revealed that patients with COVID-19 were more likely to have comorbidities of diabetes (38% versus 16%) and pancreatic insufficiency (96% versus 66%) and were less likely to be taking a CFTR modulator (46% versus 65%). The larger proportion of pwCF who had diabetes in the COVID-19 positive group is consistent with diabetes being a risk factor for symptomatic and severe COVID-19 infection in the general population [2]. As pancreatic insufficiency is associated with mutations resulting in more severe CF phenotypes [21], it is possible that pwCF with more severe disease may be at higher risk of contracting COVID-19.

We recognize the protective effects of CFTR modulators in correcting the underlying protein defect resulting in improved airway ciliary function, thereby reducing pulmonary exacerbations and improving lung function [22]. Fortunately, ETI was FDA-approved before the pandemic and is likely responsible for the significant reduction in pulmonary exacerbations by 51% in 2020 compared to 2019 [11,20]. The proportion of patients on ETI did not differ statistically between pwCF with and without a positive COVID-19 PCR and antibody test, possibly due to small sample size. However, the lower proportion of pwCF on CFTR modulator therapy (including all CFTR modulators) in the COVID-19 positive group may signify decreased frequency of symptomatic COVID-19 consistent with the known benefit of CFTR modulator therapy of decreasing pulmonary CF exacerbations [22].

Out of 26 distinct pwCF who tested positive for COVID-19, 2 (8%) were hospitalized: 1 with ACFLD and 1 post-lung transplant. 1 death was observed in the post-transplant patient. 82% (9/11) of symptomatic patients did not require hospitalization, far lower than in the ECFSPR data, which had a hospital admission rate of 58% and an ICU admission rate of 9.2%, both higher than the general population for all age groups [10].

COVID-19 IgG was found in 12.2% (18/147) of patients, of whom only 28% (5/18) reported symptoms. Of the 5 symptomatic patients, 1 had known COVID-19, 1 was tested for suspected COVID-19, and 3 were tested for routine screening. Most COVID-19 CF patients (58%, 15/26) were asymptomatic and diagnosed through antibody screening (72%, 13/18). The high specificity of the IgG assays makes the likelihood of false positives low and asymptomatic infection has been widely reported with an estimated prevalence rate of 35% based on a meta-analysis [22]. 2.7% seroprevalence was found in the Belgium CF population from April to May 2020 [23–24].

The most likely explanation for the lower prevalence of COVID-19 among pwCF in our cohort compared to general NYC population may be related to social isolation and masking practices already familiar to many pwCF. Nonetheless, the unexpectedly high number of asymptomatic cases and less severe clinical course of COVID-19 raises the question of whether pathophysiology of CF could be...
Table 3
Clinical features of COVID-19 infection in patients with cystic fibrosis.4

| Assay Type                          | Count (%) |
|-------------------------------------|-----------|
| COVID-19 PCR Positive               | 13        |
| COVID-19 IgG Antibody Positive      | 18        |
| Either PCR or IgG Antibody Positive | 26        |

| Suspected Source of COVID-19 Infection | Count (%) |
|----------------------------------------|-----------|
| Household                              | 15 (56%)  |
| Workplace                              | 1 (4%)    |
| Transportation                         | 0 (0%)    |
| Unknown                                | 10 (37%)  |

| Reason for Antibody Testing | Count (%) |
|-----------------------------|-----------|
| Routine Screening           | 12 (67%)  |
| Known COVID-19 Case         | 2 (11%)   |
| Suspected COVID-19 Case     | 3 (17%)   |
| Unknown                     | 1 (6%)    |

| Symptoms at Time of COVID-19 Infection | Count (%) |
|----------------------------------------|-----------|
| Asymptomatic                           | 15 (58%)  |
| Cough                                  | 9 (35%)   |
| Shortness of Breath                    | 7 (27%)   |
| Fever                                  | 6 (23%)   |
| Myalgia                                | 6 (23%)   |
| Spatium                                | 5 (19%)   |
| Diarrhoe                               | 3 (12%)   |
| Loss of Taste                          | 1 (4%)    |
| Chest Pain                             | 0 (0%)    |

| Treatment                               | Count (%) |
|-----------------------------------------|-----------|
| Observation Only                        | 22 (85%)  |
| New Supplemental Oxygen                 | 3 (12%)   |
| Oral Antibiotics                        | 3 (12%)   |
| Intravenous Antibiotics                 | 2 (8%)    |
| Oral Corticosteroids                    | 2 (8%)    |
| Prophylaxis-dose Anticoagulation        | 2 (8%)    |
| Pulldose Anticoagulation                | 2 (8%)    |
| Hydroxychloroquine                      | 2 (8%)    |
| Remdesivir                              | 1 (4%)    |
| Immunomodulators                        | 1 (4%)    |
| Convalescent                            | 0 (0%)    |

| Outcomes                                 | Count (%) |
|------------------------------------------|-----------|
| COVID-19 Infection Managed at Home       | 24 (92%)  |
| Symptomatic COVID-19 (N = 11) Managed at Home | 9 (82%) |
| Hospitalization for COVID-19             | 2 (8%)    |
| Intensive Care Unit Admission            | 2 (8%)    |
| Noninvasive Ventilation                  | 2 (8%)    |
| Mechanical Ventilation                   | 1 (4%)    |
| Death                                    | 1 (4%)    |

4 Data are summarized as n (%).

protective. COVID-19 results from SARS-CoV-2 infection via binding to angiotensin-converting enzyme 2 (ACE2) which is highly expressed in lung alveolar type II epithelial cells, the gastrointestinal tract, vascular endothelial cells, and brain, renal and cardiovascular tissues [25–27]. CF airway epithelial cells have increased ACE2 expression which may increase SARS-CoV-2 binding but also lead to reduced inflammation through increased Angiotensin 1–7 levels [28–29]. Serine protease TMPRSS2 also facilitates SARS-CoV-2 entry however TMPRSS2 levels are low in CF airway cells and may reduce viral entry [29]. Long-term vascular endothelial damage in CF has been associated with reduced ACE2 expression which may play a role in limiting viral spread within the host [30]. pwCF are also more vulnerable to common cold viruses which may result in high IgG to human coronaviruses and be protective against severe COVID-19 [17]. These factors are hypothetical; and the most likely explanation for the lower prevalence of COVID-19 in pwCF compared to the general population remains the practice of social isolation and masking.

Our study is limited by retrospective data collection, COVID-19 PCR and antibody testing availability, the presence of asymptomatic illness, and the effects of social isolation and self-quarantine. Due to limitations in testing and presence of asymptomatic illness, COVID-19 was likely underdiagnosed during the first months of the pandemic and therefore the prevalence is likely underestimated in our cohort. Only 152 of 810 patients underwent PCR testing and 147 of 810 patients had antibody screening. Additionally, in our post-hoc analysis comparing the clinical features of patients with CF who tested positive for COVID-19 and those who did not, our results are similarly limited by the likely presence of asymptomatic infections among patients without a positive test. Due to data inaccessibility to age categories of positive cases within the general population, we were not able to make age comparisons to our COVID-19 cohort. Asymptomatic status may be influenced by recall bias and difficulty distinguishing CF symptoms from those of COVID-19.

The COVID-19 pandemic delayed routine care, pulmonary function testing, imaging, and laboratory testing. Total clinical encounters were also reduced by 17% in 2020 compared to 2019 but this decrease could have been far worse without telehealth implementation. Delivery of care continues to integrate the use of telehealth and home monitoring such as home spirometers made available by the CF Foundation during the pandemic. Mental health screening remains crucial with amplified anxiety reported during the pandemic [31–32]. This study reflects real-world data and to our knowledge, is the only large American cohort study examining COVID-19 in the CF population.

Conclusion

CF may increase risk of complications from COVID-19, however it is reassuring that our study demonstrates a lower prevalence of COVID-19 compared to the general population in the NY metropolitan area as well as a low hospitalization rate during the first wave of the pandemic. Further studies are needed to better understand the long-term impact of COVID-19 on pwCF as the overall population becomes vaccinated and social contact returns to normal.

Authors' contributions

Joseph L. Simonson: Conceptualization, Methodology, Investigation, Data Curation, Formal Analysis, Project Administration, Writing – original draft, Writing – review and editing. Christine Esposito: Conceptualization, Investigation, Data Curation, Writing – review and editing. Theresa Frantzen: Conceptualization, Investigation, Data Curation, Writing – review and editing. Katherine Henthorne: Conceptualization, Investigation, Data Curation, Writing – review and editing. Serena Romano: Conceptualization, Investigation, Data Curation, Writing – review and editing. Aileen Espinal: Conceptualization, Investigation, Data Curation, Project Administration, Writing – review and editing. Ramona Ramdeo: Conceptualization, Investigation, Data Curation, Project Administration, Writing – review and editing. Jessica Trentacoste: Conceptualization, Investigation, Data Curation, Writing – review and editing. Donna Tsang: Conceptualization, Investigation, Data Curation, Writing – review and editing. Geralyn La Vecchia: Conceptualization, Investigation, Data Curation, Writing – review and editing. Robert Abdullah: Conceptualization, Methodology, Investigation, Writing – review and editing. Maria Berdella: Conceptualization, Methodology, Investigation, Writing – review and editing. Lynn Bonitz: Conceptualization, Investigation, Data Curation, Writing – review and editing. Andrei Constantinescu: Conceptualization, Methodology, Investigation, Writing – review and editing. Emily DiMango: Conceptualization, Methodology, Investigation, Writing – review and editing. Myah Draine: Conceptualization, Investigation, Data Curation, Writing – review and editing. Tara Gimelli: Conceptualization, Investigation, Data Curation, Writing – review and editing.
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