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Original Article

Impact of COVID-19 infection on lung function and nutritional status amongst individuals with cystic fibrosis: A global cohort study

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ABSTRACT

Background: Factors associated with severe COVID-19 infection have been identified; however, the impact of infection on longer-term outcomes is unclear. The objective of this study was to examine the impact of COVID-19 infection on the trajectory of lung function and nutritional status in people with cystic fibrosis (pwCF).
Methods: This is a retrospective global cohort study of pwCF who had confirmed COVID-19 infection diagnosed between January 1, 2020 and December 31, 2021. Forced expiratory volume in one second percent predicted ($ppFEV_1$) and body mass index (BMI) twelve months prior to and following a diagnosis of COVID-19 were recorded. Change in mean $ppFEV_1$ and BMI were compared using a *t*-test. A linear mixed-effects model was used to estimate change over time and to compare the rate of change before and after infection.
Results: A total of 6,500 cases of COVID-19 in pwCF from 33 countries were included for analysis. The mean difference in $ppFEV_1$ pre- and post-infection was 1.4 %, (95 % CI 1.1, 1.7). In those not on modulators, the difference in rate of change pre- and post-infection was 1.34 %, (95 % CI -0.88, 3.56) per year ($p = 0.24$) and -0.74 % (-1.89, 0.41) per year ($p = 0.21$) for those on elexacaftor/tezacaftor/ivacaftor. No clinically significant change was noted in BMI or BMI percentile before and after COVID-19 infection.
Conclusions: No clinically meaningful impact on lung function and BMI trajectory in the year following infection with COVID-19 was identified. This work highlights the ability of the global CF community to unify and address critical issues facing pwCF.

Introduction

Cystic fibrosis (CF) is a multisystem genetic condition that affects over 100,000 individuals globally, primarily affecting the respiratory and gastrointestinal system [1]. Although chronic bacterial infection of the airways is common in CF, superimposed viral infections can result in significant morbidity as shown by Viviani et al. following the H1N1 influenza pandemic of 2009 [2]. Among 110 individuals infected with H1N1, 48% were hospitalized and 31% required new oxygen therapy. Our knowledge of the impact of SARS-CoV-2 on the health of people with CF (pwCF) has focused primarily on describing the acute impact of the viral infection [3]. Despite literature suggesting hospitalization rates for pwCF were higher compared to the age-matched general population at the beginning of the pandemic [4], morbidity and mortality were less severe than initially feared [5–7]. Published literature from the international CF collaborations and others have identified risk factors for severe disease which include low lung function, older age, transplantation, and malnutrition [3,8,9]. Additionally, highly effective modulators (specifically, ivacaftor and elexacaftor/tezacaftor/ivacaftor) were associated with a reduced risk of hospitalization with supplemental oxygen [9].

The effect of COVID-19 infection on long-term health outcomes is less well defined. A few small studies from Italy have examined the impact of infection on pulmonary outcomes [10,11]. Colombo et al. found no significant difference in pre- and post-percent predicted forced expiratory volume in 1 second ($ppFEV_1$) following COVID-19 infection among 186 individuals with CF who were followed for a median of 61 days ($p = 0.62$). A smaller study by Medino et al. between October 2020 and June 2021 compared outcomes in 26 people with CF who were COVID-19 positive compared to 42 individuals who were COVID-19 negative and found no significant decrease in $ppFEV_1$ comparing pre and 6-months-post infection. These studies were limited by small sample sizes from a single region of the world and relatively short follow-up time. Furthermore, they examined lung function at two distinct time points and did not examine the impact of COVID on the trajectory of lung function over time.

With respect to nutritional status in pwCF following COVID-19 infection, only one study to date has provided a description of post-infection body mass index (BMI, kg/m^2) values in a cohort of 13 individuals [12]. Some studies have looked at the impact of pandemic restrictions and healthcare delivery on BMI changes in CF, but did not examine the impact of confirmed infection [13,14]. In a French study looking at outcomes related to severe COVID-19 infection in the general population, 33.3 % of survivors suffered from malnutrition at 30 days following discharge from hospital [15]. Since malnutrition is a risk factor for increased morbidity and mortality in CF, this outcome was of interest [16,17].

The objective of this study was to examine the impact of COVID-19 infection on the rate of change of both lung function and nutritional status in a large, global cohort of individuals with CF.

Methods

Study design

In March 2020, an international group of individuals representing national CF registries came together to form the CF Registry Global Collaboration in order to evaluate the impact of COVID-19 on the health of pwCF. This collaboration has since expanded to include several additional countries including those without well-established registries. This global collaboration conducted a retrospective longitudinal cohort study of individuals with CF from 47 countries who had a confirmed COVID-19 diagnosis between January 1, 2020 and December 31, 2021 (Table S1). De-identified/anonymized data were collected according to each individual nation's CF registry ethics approval or national guidelines. Data in summary tables are concealed if <6 individuals are reported by a country in a potentially identifiable category.

Data collection and variable definitions

The CF Registry Global Collaboration developed comprehensive data specifications to standardize data collection on COVID-19 infections, that were adapted into an Excel case report form and a project-specific REDCap database. Participating jurisdictions were able to use the data submission method that best suited their needs. Most countries with well-established and comprehensive CF registries extracted data from their registries as per provided data specification. The European CF Society Patient Registry (ECFSPR) collected the data with Excel forms and imputed them into a project-specific REDCap database. For most countries without well-established registries, data were collected by the CF clinics using the Excel case report form. All data was submitted using a secure file-sharing platform.

All primary COVID-19 infections were included. For individuals with multiple infections, the first diagnosis was used.

Demographic variables recorded were age at infection, sex, race, and genotype. Individuals were considered adults if they were 18 years of age or older, and pediatric if <18 years of age at the time of infection. Clinical variables obtained at the time of COVID-19 diagnosis were vaccination status, CF-related diabetes (CFRD) status (yes/no), prior history of *P. aeruginosa* infection (yes/no), pancreatic status (pancreatic insufficiency/ sufficiency), pregnancy status (yes/no), and transplant status (yes/no). Vaccination status at the time of infection was

categorized as fully, partially, not vaccinated, or unknown. Fully vaccinated was defined as the person had received all the suggested dosage(s) for a given vaccination course (for example, Jcovden® is one dose; Comirnaty® is a sequence of two) at least 14 days prior to COVID-19 infection. Partially vaccinated was defined as the person having not received all the suggested dosages of a multi-dose vaccine course or having completed the initial vaccination course <14 days before COVID-19 infection.

All available $ppFEV_1$ and BMI measurements up to 1-year prior to and 1-year following a diagnosis of COVID-19 were recorded, as well as use of CFTR modulators (CFTRm) at the time of clinical measurements. Countries submitted the $ppFEV_1$ using GLI 2012 reference equations whenever possible [18]. Extreme values of $ppFEV_1$ and BMI (less than or equal to the 0.5th or greater than or equal to the 99.5th percentile of distribution) were excluded. Body mass index percentiles (BMI percentile) were calculated for children up to 17 years of age using the Centers for Disease Control and Prevention growth charts [19]. Children were then classified as: underweight (BMI percentile $\leq$ 12 %), adequate weight (BMI percentile 13–84 % or overweight (BMI percentile $\geq$ 85 %) [20]. For individuals 18 years of age and older, subjects were classified into BMI categories based on World Health Organization guidelines as underweight (<18.5 kg/m^2), adequate weight (18.5–24.9 kg/m^2), or overweight ($\geq$ 25.0 kg/m^2) [Anon., 21]. Using World Bank definitions for 2022 fiscal year, countries with a gross national index per capita less than $12,696 were considered to be low-and-middle income countries (LMIC) and others were considered high-income countries (HIC) [Anon., 22]. CFTRm status (ivacaftor, lumacaftor/ivacaftor, tezacaftor/-ivacaftor, elexacaftor/tezacaftor/ ivacaftor (ETI)) was recorded at each clinical measurement of lung function and BMI. Where CFTRm status was missing the last observation carried forward method was used to impute later CFTRm status.

After applying exclusions, two study cohorts ($ppFEV_1$ and BMI) were created to assess the impact of COVID-19 on $ppFEV_1$ and BMI separately (Fig. 1). Two further sub-cohorts were created based on continuous use of either ETI or no CFTRm use during the study period.

Statistical analysis

Demographic, clinical characteristics, and outcome measures were summarized as frequencies and proportions for categorical variables and median with interquartile range (IQR) for continuous variables.

Subgroup analysis

Analyses were conducted separately for $ppFEV_1$ and BMI cohorts with the BMI analysis conducted separately for adults and pediatrics. For each individual, the mean $ppFEV_1$ and BMI of all available measurements 12 months prior to and after COVID-19 infection was calculated. These were summarized for each cohort and by sub-groups (defined by age, CFTRm use, baseline $ppFEV_1$ or BMI as appropriate, infection year, country income status) using mean and standard deviation (sd) and presented the mean difference with 95 % confidence intervals (95 % CI). These results were used to inform the covariates selected for the mixed-effects model.

Main analysis

While cleaning and summarising the data, complex patterns of modulator usage were identified. For example, some individuals switched from one modulator to a different modulator during the study period. In an effort to isolate the impact of the COVID-19 infection on clinical outcomes, homogenous modulator usage groups were created, specifically the no modulator and continuous ETI use group. This meant further excluding individuals who did not fit into either of these sub-groups. For example, individuals who were not on modulator therapy prior to their COVID-19 infection and then started ETI at a later date, were not included in either of these groups.

A linear mixed-effects model with a random intercept at the individual level was utilized where $ppFEV_1$ or BMI was the dependent variable of interest. The model included the following terms: fixed and random intercepts, time from infection (years), study period (pre or post COVID-19 infection) as a binary indicator, and an interaction term of study period by time. Terms for age at infection, sex, year of infection (2020 vs 2021) and country income status (High-income country vs Low-to-middle-income country) were included as time independent covariates for adjustment. Random intercepts were included at the individual level to account for correlation of repeated measurements [23]. Year of infection was included as a covariate to adjust for differences in disease severity related to different COVID variants as well as variation in testing and care strategies as the pandemic progressed. Country income status (High-income country vs Low-to-middle-income country) was added since some countries contributed too few cases to be included as an individual control variable, country income status allowed us to control for heterogeneity between groups of countries.

Results

A total of 7139 cases of COVID-19 were reported from 47 countries from January 1, 2020 to December 31, 2021. After applying exclusions (primarily due to post transplant status), a total of 6500 people were

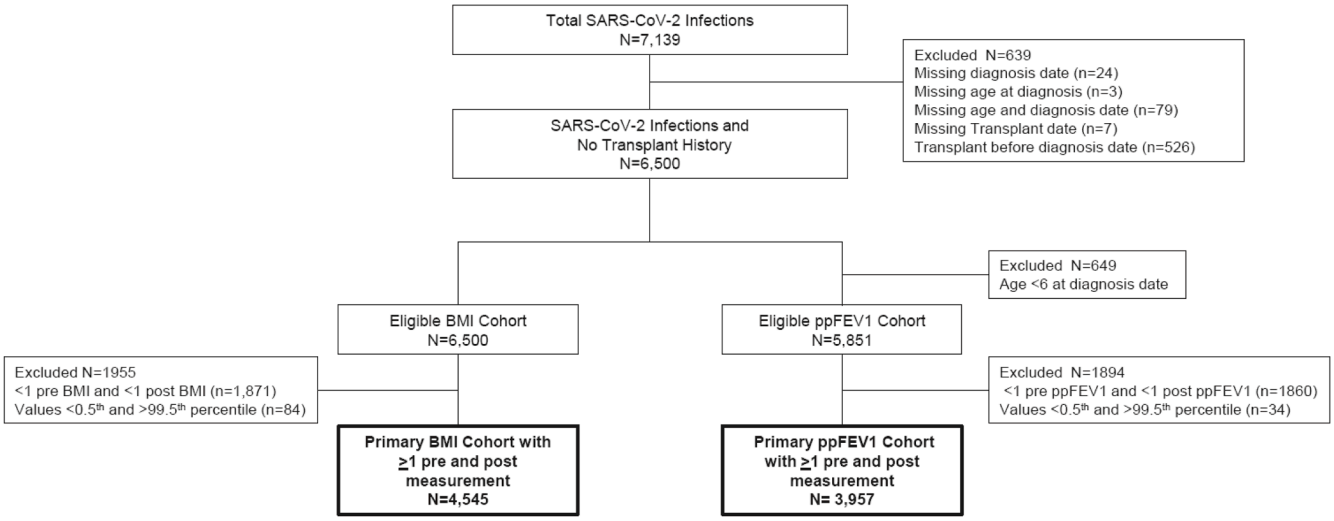

Fig. 1. Study cohort creation.

eligible for inclusion. (Fig. 1, Table S1). There were 344 (5.3 %) individuals who had a record of more than one COVID-19 infection in the study period. Diagnosis was based on RT-PCR 5038 (77.5 %), rapid antigen testing 653 (10 %), antibody serology 307 (4.7 %), chest tomography 2 (0.01 %), clinical opinion 56 (0.9 %), other 2 (0.01 %), and unknown 442 (6.8 %). Individuals required *at least* one pre- and one post-COVID-19 clinical measurement to be included the two study cohorts (FEV_1 and/or BMI analyses). Demographic and clinical characteristics for the overall cohort were similar to those in both the lung function and BMI cohorts, Table 1. Fig. 2 shows the waves in reported cases aligning with the emergence dates of COVID-19 variants such as Delta and Omicron [Anon., 24]. ETI use increased over the study period (Figure S1) while the use of non-ETI modulators decreased. There were 2196 (33.8 %) individuals not on modulators at any time point in the study period. A total of 135 (6.7 % of women of child-bearing age) women were pregnant at the time of COVID-19 infection. Twelve transplants (<1 %) were recorded following COVID-19 infection (9 lung, 3 liver). In terms of vaccination status, 976 (15.0 %) were fully vaccinated, 266 (4.1 %) were partially vaccinated, 3152 (48.5 %) were not vaccinated and 2106 (32.4 %) had unknown vaccination status at the time of infection. Data were submitted from 515 (7.9 %) individuals from countries considered LMIC.

Lung function analysis

A total of 3957 individuals from 30 countries had at least 1 pre- and post-lung function measurement and were included in the $ppFEV_1$ analysis. Lung function measurements were taken, on average, 5.9 months prior to COVID-19 infection and 5.0 months post COVID-19 infection. The average number of FEV_1 measurements per participant pre-infection was 2.8 and was 2.3 for post-infection.

Pre- and post-infection average $ppFEV_1$

The mean pre-infection $ppFEV_1$ was 79.0 versus 80.4 post-infection (difference of 1.4 %, 95 % confidence interval (CI) 1.1, 1.6). The magnitude and direction of the difference were similar across various sub-groups with the exception of individuals from LMIC countries who had a mean change in $ppFEV_1$ of −3.8 % (95 % CI −5.9, −1.8). For the sub-group not on modulators ($N = 804$) there was a small decrease in mean $ppFEV_1$ pre- and post-infection of −0.6 % (95 % CI −0.6 (−1.3, 0.0). Those on ETI ($N = 1285$) in the pre- and post-period showed no change. (Table S3)

Rate of change in $ppFEV_1$

Demographic and clinical characteristics for the FEV_1 rate of decline analytic cohort can be seen in Table S2. When examining the impact of COVID-19 on the trajectory of lung function, we evaluated the difference in the annual rate of change pre- and post-COVID-19 in those who were not on any modulator therapy throughout the study period and individuals who were recorded as on ETI in both the pre- and post-period (Table 2), in an effort to make results more interpretable. In those on ETI, the difference in the rate of change in $ppFEV_1$ before and after infection was −0.74 % (95 % CI −1.89, 0.42) per year ($p = 0.21$). In those who were not on any modulator therapy, the difference in the rate of change was 1.34 %, (95 % CI −0.88, 3.56) ($p = 0.24$). (Table 2, Fig. 3).

BMI analysis

A total of 4545 individuals (2689 adults, 1856 children) from 33 countries had at least 1 pre- and post-infection BMI measurement and could be included in the BMI analysis. BMI measurements were taken on average 5.9 months prior to infection date and 4.9 months post-infection. The average number of BMI measurements per participant pre-infection was 3.0 and was 2.4 for post-infection.

Table 1
Demographic and clinical characteristics at the time of COVID-19 infection.

	Overall $N = 6500$	FEV_1 cohort $N = 3957$	BMI cohort $N = 4545$
Sex			
Female	3221 (49.6)	2022 (51.1)	2299 (50.6)
Male	3278 (50.4)	1935 (48.9)	2246 (49.4)
Age; Median (IQR)	21.0 (11.8, 31.0)	22.3 (14.1, 32.0)	20.9 (12.0, 31.0)
Age groups			
<6	649 (10.0)	0 (0.00)	392 (8.6)
6–17	2652 (30.8)	1370 (34.6)	1474 (32.4)
18–39	3058 (47.0)	2066 (52.2)	2149 (47.3)
≥40	790 (12.2)	521 (13.2)	530 (11.7)
Race/ethnicity			
White	5679 (87.4)	3530 (89.2)	3997 (87.9)
Black	115 (1.8)	76 (1.9)	91 (2.0)
Asian	107 (1.6)	30 (0.8)	42 (0.9)
Other	555 (8.5)	306 (7.7)	396 (8.7)
Unknown	44 (0.7)	15 (0.4)	19 (0.4)
Genotype			
Heterozygous F508del	2636 (40.6)	1590 (40.2)	1787 (39.3)
Homozygous F508del	2647 (40.7)	1804 (45.6)	2053 (45.2)
Other	1090 (16.8)	516 (13.0)	642 (14.1)
Unknown	127 (2.0)	47 (1.2)	63 (1.4)
Baseline $ppFEV_1$; Median (IQR)	82.4 (62.0, 97.0)	82.0 (62.1, 96.8)	82.7 (62.7, 97.2)
Baseline $ppFEV_1$			
<40 %	344 (5.3)	261 (6.6)	278 (6.1)
40–70 %	1233 (19.0)	1050 (26.5)	1024 (22.5)
>70 %	3176 (48.9)	2646 (66.9)	2687 (59.1)
Missing	1098 (16.9)	0 (0.00)	164 (3.6)
Age at infection <6	649 (10.0)	0 (0.00)	392 (8.6)
Baseline BMI; Median (IQR)	21.3 (18.1, 24.3)	21.7 (18.9, 24.6)	21.2 (18.1, 24.2)
Baseline BMI category[1]			
Underweight	405 (6.2)	254 (6.4)	289 (6.4)
Normal	3510 (54.0)	2614 (66.1)	3056 (67.2)
Overweight	1461 (22.5)	1052 (26.6)	1200 (26.4)
Missing	1124 (17.3)	37 (0.9)	0 (0.00)
CF-related diabetes	1213 (18.7)	900 (22.7)	941 (20.7)
Missing	974 (15.0)	18 (0.5)	593 (13.0)
***P. aeruginosa* infection**[2]	3007 (46.3)	2003 (50.6)	2147 (47.2)
Missing	78 (1.2)	10 (0.3)	13 (0.3)
Pancreatic insufficiency	4384 (67.4)	2715 (68.6)	3157 (69.5)
Missing	124 (1.9)	22 (0.6)	19 (0.4)
CFTR modulators[3]			
Ivacaftor	367 (5.6)	222 (5.6)	278 (6.1)
Lumacaftor-ivacaftor	403 (6.2)	217 (5.5)	298 (6.6)
Tezacaftor-ivacaftor	272 (4.2)	223 (5.6)	224 (4.9)
Elexacaftor-tezacaftor-ivacaftor	2961 (45.6)	2305 (58.3)	2425 (53.4)
Unknown	299 (4.6)	0 (0.00)	0 (0.00)
Pregnant[4]	135 (6.7)	110 (7.8)	112 (7.7)
Country income status			
LMIC	515 (7.9)	113 (2.9)	173 (3.8)
HIC	5985 (92.1)	3844 (97.1)	4372 (96.2)
SARS-CoV2 Vaccination status			
Fully vaccinated	976 (15.0)	630 (15.9)	666 (14.7)
Partially vaccinated	266 (4.1)	165 (4.2)	172 (3.8)
Unvaccinated	3152 (48.5)	2086 (52.7)	2312 (50.9)
Unknown	2106 (32.4)	1076 (27.2)	1395 (30.7)

Values are n (%) unless otherwise specified. Proportions are calculated from column totals (n/N) Where no 'Missing' row is included, variables are 100 % complete.

Abbreviations; IQR, interquartile range; CFTR, cystic fibrosis transmembrane conductance regulator; $ppFEV_1$, percent predicted forced expiratory volume in 1 s; LMIC, low-and-middle-income country; HIC, high-income country.

[1] BMI categories are defined according to WHO guidelines. People aged <19 years classified as underweight (percentile ≤12 %), normal (percentile 13–84 %) or overweight (percentile ≥85 %). People aged ≥19 years classified as underweight (BMI <18.5 kg/m^2), normal (18.5–24.9 kg/m^2) or overweight ((≥ 25.0 kg/m^2).

[2] Chronic or intermittent infection in the 5 years prior to COVID-19 diagnosis.

[3] Using CFTR modulators at the time of COVID-19 diagnosis.

[4] The denominator was defined as being female and age at infection ≥14 and ≤50 years.

Pre- and post-BMI

For the adult cohort, mean BMI prior to infection was 23.7 kg/m^2 and increased to 24.1 kg/m^2 post-infection with a mean difference of 0.4 kg/m^2 (95 % CI 0.3, 0.4). For the pediatric cohort, mean BMI percentile was 56.0 % pre-infection and increased to 58.9 % post-infection representing a mean change of 2.9 % (95 % CI 2.2, 3.5). The magnitude and direction of the difference were similar across various sub-groups except for those who were considered underweight at the time of infection. This group had a mean change in BMI percentile of 7.5 % (95 % CI 5.5, 0.5) (Table S3).

Rate of change in BMI

Demographic and clinical characteristics for the adult and pediatric BMI rate of decline analytic cohort can be seen in Table S2. A rate of change analysis was completed for both the adult and pediatric cohort separately with results summarized in Table 2 and Fig. 3. For adults who were on ETI throughout the study period, the positive rate of change in BMI was attenuated following COVID-19 with a mean difference in slope of −0.32 kg/m^2/year (95 % CI −0.56, −0.068; $p = 0.01$). A similar picture was seen in the pediatric cohort with a mean difference in slope of −4.16%/year (95 % CI −7.76, −0.56; $p = 0.02$). In contrast, there was no difference in slope in the cohort not using modulator therapy in the adult or pediatric cohorts.

Additional analyses

Further, vaccination status, sex and country income did not modify the impact of infection on lung function or BMI trajectory. Separate sensitivity analyses excluded individuals with multiple records of infection as well as those diagnosed with COVID-19 by antibody serology, chest CT and clinical opinion and our results were unchanged (data not shown).

Discussion

In this global observational study, we assessed the impact of COVID-19 infection on the progression of CF pulmonary disease and nutritional status in a large CF population over a 1-year follow-up period. Reassuringly, we found no clinically meaningful negative impact in lung function or BMI following infection.

To our knowledge, there have been no previous studies specifically examining the impact that COVID-19 infection has on the trajectory of lung function and nutritional status in CF. The difference in the rate of change in ppFEV$_1$ pre- and post-infection was not statistically significant in either of the two groups examined (i.e., the no modulator group or the ETI group). In those pwCF not on a modulator, there was a statistically and clinically significant decline in lung function over time in the pre-pandemic period. This was attenuated in the post-pandemic period such that the decline in lung function was no longer statistically significantly different from zero. This finding could be secondary to the pandemic restrictions (i.e. hand hygiene, isolation, and masks) resulting in reduced exposure to all respiratory viruses and thus fewer pulmonary exacerbations which are known to be associated with lung function decline [25,26]. Alternatively, it could reflect a 2 -year observation period with any population change less than the variability in the measurement of lung function within a group. The ETI group did not have a significant decline in either the pre- or the post-period. One possible explanation for the pattern seen in the ETI group may be linked to the initial improvements in lung function seen with the start of ETI therapy which happen on average within a few weeks of starting the medication and then stabilizes over time [27]. Individuals who were on ETI in the pre-pandemic period would have started the medication recently as it only became available in the US (the country that contributed the largest sample) several months prior to the onset of the pandemic. The initial impact on lung function would be captured in our study time period and may obscure any decline in lung function otherwise seen.

Our results are consistent with prior literature showing minimal change in ppFEV$_1$ following COVID-19 in the CF population [10,11]. In a smaller cohort of individuals with CF in Italy who had confirmed COVID-19 and were managed at home, Terlizzi et al. found 62 % (8/13) individuals had stable or improving ppFEV$_1$ following infection however, these were mild cases given they were managed as outpatients [12]. Doumit et al. examined the overall trend in lung function in the CF population before and after the pandemic began and found improvements in lung function in the post-pandemic period [13]. We chose to look at ppFEV$_1$ as a marker of lung function given its established role in disease progression and consistent associations with pulmonary exacerbations, hospitalizations, as well as morbidity and mortality [28–30]. With respect to other lung function parameters, one study in non-CF population examining outcomes in COVID-19 showed impairment in diffusing capacity (DLCO) and forced vital capacity (FVC) following infection that then improved in the 6 month – 1 year post-infection

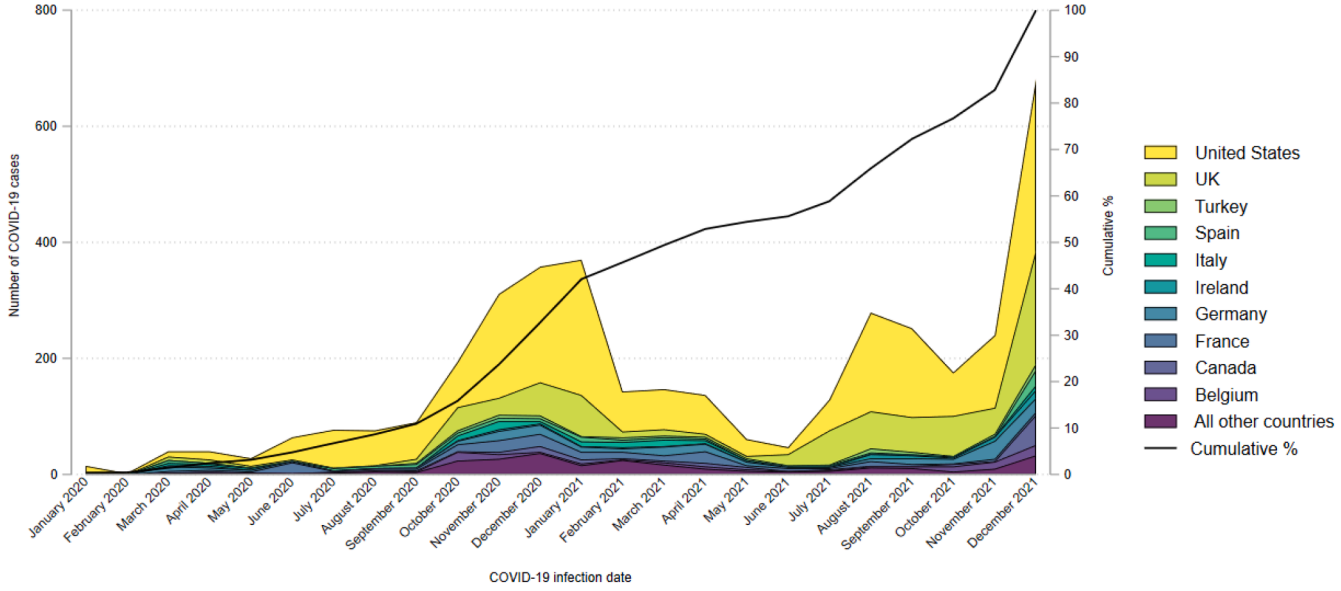

Fig. 2. The number of COVID-19 infections over time.

Table 2
Rate of change analyses for ppFEV$_1$ and BMI following COVID-19 infection.

Lung Function Cohort	N	Pre-infection slope (ppFEV$_1$/year)	Post-infection slope (ppFEV$_1$/year)	Slope difference (ppFEV$_1$/year)	Slope difference p value
No Modulators	804	−1.55 (−2.98, −0.13)	−0.21 (−1.48, 1.42)	1.34 (−0.88, 3.56)	0.24
ETI Only	1285	0.67 (−0.038, 1.37)	−0.085 (−0.98, 0.83)	−0.74 (−1.89, 0.41)	0.20
BMI Adult Cohort[1]	**N**	**Pre-infection slope** (BMI kg/m^2/year)	**Post -infection slope** (BMI kg/m^2)/year)	**Slope difference** (BMI kg/m^2/year)	**Slope difference p value**
No Modulators	461	0.049 (−0.17, 0.27)	−0.12 (−0.36, 0.12)	−0.17 (−0.50, 0.17)	0.33
ETI Only	1099	0.56 (0.42, 0.71)	0.25 (0.05, 0.45)	−0.32 (−0.56, −0.07)	0.01
BMI Pediatric Cohort[2]	**N**	**Pre-infection slope** (BMI percentile/year)	**Post-infection slope** (BMI percentile/year)	**Slope difference** (BMI percentile/year)	**Slope difference p value**
No Modulators	642	2.11 (−0.22, 4.43)	1.77 (−1.03, 4.58)	−0.33 (−4.03, 3.37)	0.86
ETI Only	235	6.01 (3.85, 8.16)	1.84 (−1.06, 4.7)	−4.16 (−7.76, −0.56)	0.02

All rate of change analyses were adjusted for sex, age, infection year, and income status of country and the Wald test from the interaction term used to compute p-values. *Abbreviations*: ppFEV$_1$, percent predicted forced expiratory volume in 1 second; BMI, body mass index; ETI, elexacaftor/tezacaftor/ivacaftor.

[1] The adult cohort included individuals aged 18 years and above.

[2] The pediatric cohort included individuals less than age 18 years.

period [31]. There was an unexpected decline in years 1 to 2 in both DLCO and TLC [32]. However, a recent longitudinal study examining the three-year outcomes revealed that individuals with prior infection showed no significant change in FEV$_1$, FVC, TLC, or DLCO when compared to matched healthy controls [33].

Literature on BMI changes following infection with COVID-19 is limited. We did not find any clinically meaningful change in mean BMI or BMI percentile pre- and post-infection with COVID-19 in our adult and pediatric cohorts. However, there was a statistically significant attenuation of the rate of change in nutritional status before and after infection seen only in the ETI group amongst both the adults and the pediatric cohorts. This attenuation likely represents a plateauing that follows the increase in weight seen after initiating ETI, likely unrelated to the COVID-19 infection.

One of the main strengths of this study is its global representation of the impact of COVID-19 on the health of people living with CF including many countries traditionally not well represented in the published CF literature. To our knowledge, this is the largest cohort reporting outcomes related to COVID-19 in CF. Whereas most studies to date have focused on the risks associated with severe acute disease [3], our study provides novel information on the impact of this virus on the trajectory of clinically important outcomes in CF. We implemented a standardized data collection template, with clear variable definitions, and adapted it to allow multiple methods of data collection.

We must also acknowledge several limitations. First, a significant number of individuals were excluded from the FEV$_1$ and BMI cohort due to missing data – predominantly in the outcome of interest in the respective cohorts, which could influence statistical test results. However, despite this, our final sample size was large, geographically diverse and inclusive of people across the spectrum of disease severity. Further, the demographics of the excluded cohort were similar to those included in the final analysis (data not shown). The simultaneous occurrence of the pandemic and the availability of ETI significantly confounded our outcomes due to the fact that ETI is known to enhance lung function and BMI. We did not have exact start dates for ETI initiation but only whether the individual was on a modulator at the time of the clinical measurement. However, we attempted to minimize this effect by analyzing outcomes in a group without modulators and those on ETI during the entire observation period. Although it is possible baseline ppFEV$_1$ or BMI interact with COVID-19 infection to influence outcomes, we do not know if the values collected represented the individual's true baseline therefore we were unable to conduct analyses to robustly answer this question with our study. Our study only evaluated the impact of COVID-19 on ppFEV$_1$, and therefore the effects on other lung function parameters such as DLCO or TLC are unknown. Our study was limited to data up to one year following COVID-19 infection and therefore the longer-term impacts remain unknown. However, the impact of infection would be expected to have its maximum effect within the first 12 months of exposure. Although the changes in trajectory of lung function and BMI were different in the ETI and no modulator cohorts, the purpose of our study was not to statistically compare these results and therefore the significance of this is unclear. Finally, given the observational nature of the study, there may be confounding factors such as COVID specific therapies or the presence of respiratory comorbidities that we were unable to control for in these analyses.

In summary, we used a large, diverse cohort of individuals living with cystic fibrosis to examine the impact of COVID-19 on lung function and BMI trajectories. Our findings suggest that COVID-19 infection does not have a clinically meaningful impact on lung function or BMI trajectory in the year following infection. Future studies are needed to characterize the impacts of COVID-19 on other metrics beyond BMI and ppFEV$_1$ in the CF population. This work highlights the ability of the global CF community to unify to address critical issues facing people with CF.

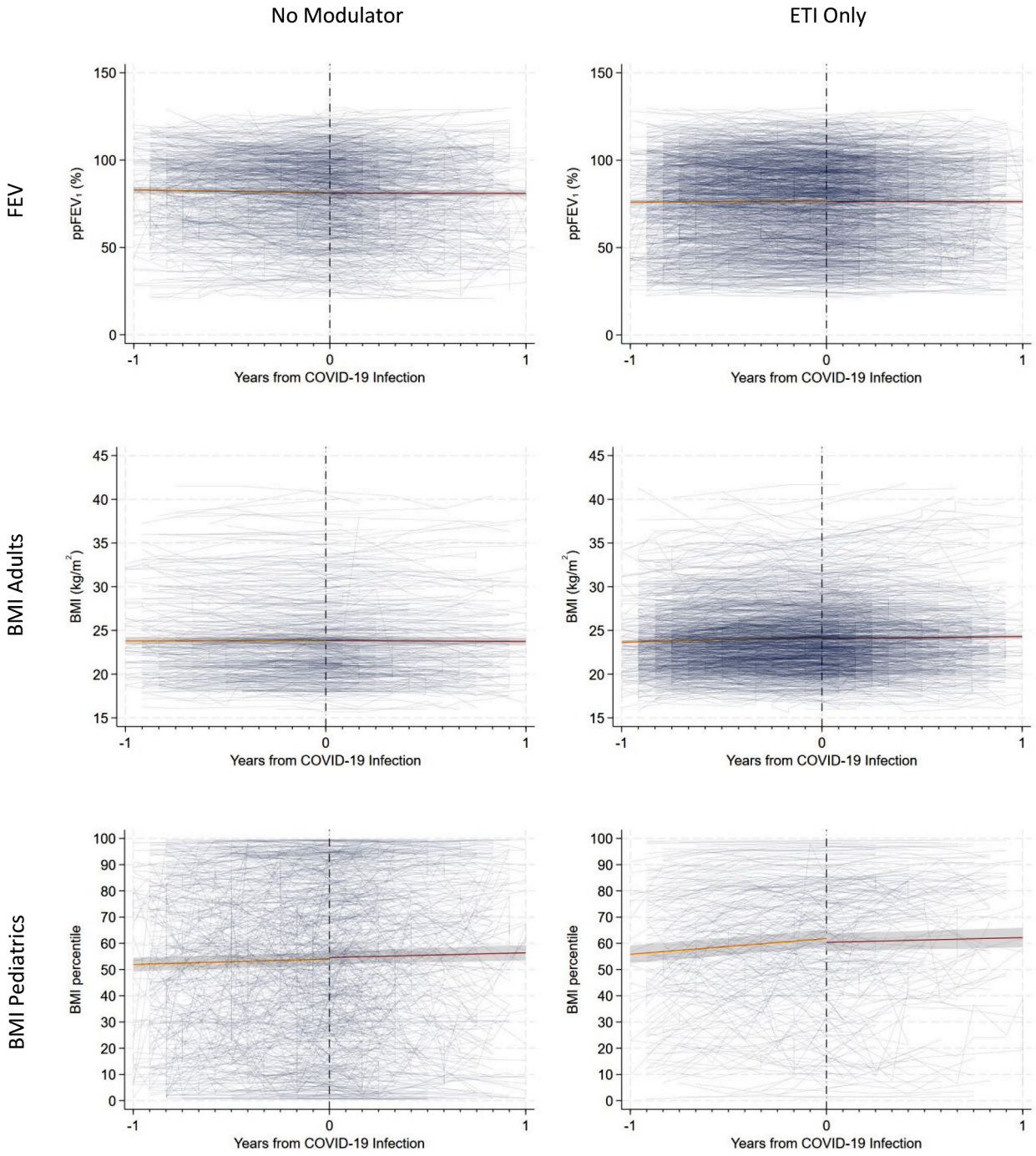

Fig. 3. Rate of change in $ppFEV_1$ and BMI/BMI percentile pre- and post-COVID-19 infection by modulator status.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

The authors of this manuscript receive funding in the form of consulting fees or honoraria from Vertex Pharmaceuticals, Chiesi Pharmaceuticals, Enterprise Therapeutics, Gilead Sciences, GSK, AstraZeneca, Insmed, MSD, Sanofi, Viartis, Zambon, Limbic, Effrx Pharmaceuticals and Omron. Additionally, there is an author who serves on the Novartis Data and Safety Monitoring Board.

There are several authors who are employed by the Cystic Fibrosis Foundation (CFF). The CFF, to advance drug development and search for a cure, have contracts with several companies to help fund the development of potential treatments and/or cures for cystic fibrosis. Pursuant to these contracts, CFF may receive milestone-based payments, equity interests, royalties on the net sales of therapies, and/or other forms of consideration. Resulting revenue received by CFF is used in support of our mission.

See "How Drugs Get on the Pipeline" on the CFF website for more information.

Additionally, CFF may license CFF Patient Registry data to some companies to monitor drug safety as part of the U.S. Food and Drug Administration's required Phase 4 clinical trials process and to encourage research aimed at improving the care of people with CF, while maintaining our obligation and commitment to protect the privacy of Registry participants. In connection with these licenses, and

upon request, CFF may also assist company researchers in interpreting CFF Patient Registry data to aid in designing, analyzing, and interpreting real world studies in CF.

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Author contributions

Study concept and design: ALS, SYC
Analysis and interpretation of data: All
Drafting of the manuscript: JS, ALS, SCC, YN, SYC
Critical revision of the manuscript for important intellectual content: All
Statistical analysis: SCC, YN
Study supervision: ALS

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Supplementary materials

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