Factors associated with clinical progression to severe COVID-19 in people with cystic fibrosis: a global observational study

Siobhán B Carr[1,2]*, Elliot McClenaghan[3,4]*, Alexander Elbert[5]*, Albert Faro[5], Rebecca Cosgriff[3], Olzhas Abdrakhmanov[6], Keith Brownlee[3], Pierre-Régis Burgel[7], Catherine A Byrnes[8], Stephanie Cheng[9], Carla Columbo[10], Harriet Corvol[11], Géraldine Daneau[12], Christopher H Goss[13], Vincent Gulmans[14], Hector Gutierrez[15], Satenik Harutyunyan[16], Andreas Jung[17], Nataliya Kashirskaya[18], Edward McKone[19], Joel Melo[20], Peter G Middleton[21], Pedro Mondejar-Lopez[22], Isabelle de Monestrol[23], Lutz Nährlich[24], Rita Padoan[25], Megan Parker[9], M Dolores Pastor-Vivero[26], Samar Rizvi[5], Rasa Ruseckaite[27], Marco Salvatore[28], Luiz Vicente R F da Silva-Filho[29], Nick Vermessen[30], Marco Zampoli[31], Anne L Stephenson[9,32#], Bruce C Marshall[5#] on behalf of the Global Registries CF Collaboration

1) Royal Brompton Hospital, part of GSST NHS Foundation Trust, London, UK
2) NHLI, Imperial College, London, UK
3) Cystic Fibrosis Trust, London, UK
4) London School of Hygiene and Tropical Medicine, London, UK
5) Cystic Fibrosis Foundation, USA
6) The Second Children's Hospital, Kazakhstan
7) Université de Paris, Inserm U1016, Institut Cochin and Cochin Hospital, Assistance Publique Hôpitaux de Paris (APHP), France
8) Starship Children's Hospital and University of Auckland, Auckland, New Zealand
9) Cystic Fibrosis Canada
10) Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Italy
11) Sorbonne Université, Inserm, Centre de Recherche Saint-Antoine, Assistance Publique Hôpitaux de Paris (APHP), Hôpital Trousseau, Service de Pneumologie Pédiatrique, Paris, France
12) Sciensano, Belgium
13) University of Washington, Seattle, USA
14) Dutch CF Foundation NCFS, Baarn, Netherlands
15) University of Alabama at Birmingham, Alabama, USA
16) Yerevan University CF Centre, Muratsan Hospital, Yerevan, Armenia
17) University Children's Hospital, Zurich, Switzerland
18) Research Centre for Medical Genetics, Russia
19) St Vincent's University Hospital, Dublin, Ireland
20) Instituto Nacional Del Torax, Chile
21) Westmead Hospital, Sydney, Australia
22) Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain
23) Department of Pediatrics, CLINTEC, Karolinska Institutet; Karolinska University Hospital Huddinge, Sweden
24) Department of Pediatrics, Justus-Liebig-University Giessen, Giessen, Germany
25) Cystic Fibrosis Support Center, Department of Paediatric, University of Brescia, Italy
26) Hospital Universitario Cruces, IIC Biocruces-Bizkaia, Bizkaia
27) Monash University, Melbourne, Australia
28) National Center Rare Diseases/Istituto Superiore di Sanità, Rome, Italy
29) Instituto da Criança HCFMUSP, São Paulo, Brazil
30) Expert by Experience
31) University of Cape Town and Red Cross War Memorial Children's Hospital, South Africa
32) Toronto Adult Cystic Fibrosis Centre, St. Michael's Hospital, Toronto, Canada

*Joint first authors
Joint last authors

Abstract

Background

This international study aimed to characterise the impact of acute SARS-CoV-2 infection in people with cystic fibrosis and investigate factors associated with severe outcomes.

Methods

Data from 22 countries prior to 13th December 2020 and the introduction of vaccines were included. It was de-identified and included patient demographics, clinical characteristics, treatments, outcomes and sequalae following SARS-CoV-2 infection. Multivariable logistic regression was used to investigate factors associated with clinical progression to severe COVID-19, using the primary outcome of hospitalisation with supplemental oxygen.

Findings:

SARS-CoV-2 was reported in 1555 people with CF, 1452 were included in the analysis. One third were aged <18 years, and 9.4% were solid-organ transplant recipients. 74.5% were symptomatic and 22% were admitted to hospital. Transplanted patients were hospitalised with supplemental oxygen therapy (21.9%) more often than non-transplanted (8.8%) and was independently associated with the primary outcome (Adjusted OR 2.45 95%CI 1.27-4.71 p=0.007). In the non-transplanted cohort, 39.5% of patients with ppFEV1<40% were hospitalised with oxygen verses 3.2% with ppFEV >70%: a 17-fold increase in odds. Worse outcomes were independently associated with older age, non-white race, underweight body mass index, and CF-related diabetes. Prescription of highly effective CFTR modulator therapies was associated with a significantly reduced odds of being hospitalised with oxygen (AOR 0.43 95%CI 0.31-0.60 p<0.001).

Interpretation:

This is the first study to show that there is a protective effect from the use of CFTR modulator therapy and that people with CF from an ethnic minority are at more risk of severe infection with SARS-CoV-2.

Funding: none

Introduction

Cystic fibrosis (CF) is a rare inherited multi-organ condition affecting people from around the globe(1). It is life limiting with a progressive decline in lung health characterised by recurrent respiratory infections and pulmonary exacerbations, which can be triggered by respiratory viruses. These require frequent hospital admissions for aggressive antibiotic therapy in up to 50% of adults with CF each year(2). In recent years new disease modifying drugs in the form of CF transmembrane conductance regulator modulator therapies (CFTRm) have been introduced that appear to have an impact on the disease course of CF(3).

Definitions of severe SARS-CoV-2 infection are generally denoted as clinical sequalae such as need for supplemental oxygen therapy, intensive care, ventilation, and death(4). Defining severe SARS-CoV-2 is challenging in people with CF. They are often hospitalised during pulmonary exacerbations for intensive treatment with antibiotics. Ten percent will use non-invasive ventilation (NIV) over the course of their lifetime because of their underlying chronic illness(5) with 2.4% currently reported as using it in the US and between 7 and 11% using long term oxygen therapy over the last few years(6).

Due to the relatively low absolute number of infections reported in people with CF during the first nine months of the pandemic, existing literature was largely descriptive(7)(8). The first wave of the pandemic in Europe showed that people with CF are more frequently hospitalised due to SARS-CoV-

2 infection than the age-matched general population infected with SARS-CoV-2(9). Within the CF population infected with SARS-CoV-2, higher proportions with advanced lung disease, CF related diabetes (CFRD) or recipients of a solid organ transplant were admitted to hospital(10). There remains a need to characterise SARS-CoV-2 infection in people with CF globally, and to better understand factors influencing more severe outcomes and more clinically vulnerable sub-groups within this population.

Since the pandemic was declared in March 2020, the CF Registry Global Collaboration (formerly the CF Registry Global Harmonisation Group) has met regularly to monitor and report on cases in people with CF worldwide. A peer reviewed rapid publication was released May 2020 that documented the first 40 cases of SARS-CoV-2(7) follow-up a few months later in 2020 with a slightly larger cohort(8). The group has continued to track the impact of this infection in the global CF community, shown paediatric cases in the CF population appear to be less severe than in adults(11), and lobbied to recommend people with CF are prioritised for vaccination(12).

This study aims to characterise the impact of acute SARS-CoV-2 infection in people with CF and investigate possible risk and protective factors associated with severe SARS-CoV-2 infection. As indications for hospitalization may vary in different healthcare systems, in this study severe infection is defined as hospitalisation requiring additional or new supplemental oxygen.

Methods

Study design and population

The 22 countries currently forming the CF Registry Global Collaboration (Supplementary table 1) cover a total global CF population of over 88,000 people. Data on cases of SARS-CoV-2 were collected through established CF registries or through a mix of retrospective and prospective case reports in adherence to a standardised data collection template agreed upon by an expert clinical group and the CF Registry Global Collaboration.

All confirmed diagnoses of SARS-CoV-2 infection diagnosed between 1st February 2020 and 13th December 2020 were eligible for inclusion in the study, including the 181 previously reported by the collaboration. The Covid-19 cohort described in this study includes several large countries outside of Europe that contributed over half of the cohort. All but one participating country in the study reported cases. SARS-CoV-2 cases known to CF teams and diagnosed by RT-PCR, antigen/lateral flow test, or confirmed by medical team consensus were included.

Ethical considerations/data governance

De-identified data were collected according to each individual nation's CF registry ethics approval or national guidelines.

Variables

Demographic characteristics defined at diagnosis of SARS-CoV-2 included age, sex, race, CFTR genotype, pregnancy and transplant status. Baseline clinical characteristics in the year prior to diagnosis of SARS-CoV-2 included lung function as recorded by the best forced expiratory volume in one second percent predicted (ppFEV$_1$, Global Lung Function Initiative (GLI) equations), body mass index (BMI), CFRD as defined by prescription of insulin therapy, *Pseudomonas aeruginosa* infection (intermittent or chronic infection), pancreatic insufficiency, systemic hypertension, and prescription of CFTRm at the time of SARS-CoV-2 diagnosis. The four available CFTRm, which are subject to varying access across countries, were categorised into highly effective (ivacaftor or combination elexacaftor/tezacaftor/ivacaftor) and effective (combination lumacaftor/ivacaftor or combination tezacaftor/ivacaftor).

BMI values were converted to percentiles in patients aged ≤18 years according to Centers for Disease Control and Prevention (CDC) reference values. BMI was then reported and analysed as a categorical variable to allow the paediatric and adult patients to be analysed together. People aged <19 years were classified as underweight (percentile ≤12%), normal (percentile 13-84%) or overweight (percentile ≥85%). People aged ≥19 years were classified as underweight (BMI <18.5 kg/m^2), normal (18.5-24.9 kg/m^2) or overweight ((≥ 25.0 kg/m^2), according to WHO guidelines(13).

Race was collected in 4 categories: white, black, Asian, and other. Due to variations in how racial groups are defined across countries and low numbers in non-white groups the multivariable analysis combined categories to white and non-white. It should be noted that those of Hispanic ethnicity were recorded as white race, in the US this made up 13 % of their cohort. In recognition of the clinical differences between the pre- and post-transplant CF condition, summary statistics were stratified by solid organ transplant status.

Outcomes

The primary outcome of severe SARS-CoV-2 infection as defined by hospitalisation with requirement for new or additional supplemental oxygen therapy, corresponds to level 4 in the WHO COVID-19 clinical progression matrix(14). Secondary outcomes of interest included hospitalisation, additional NIV use, intensive care unit (ICU) admission and death. Deaths were reported as all-cause mortality within 3 months of SARS-CoV-2 diagnosis, and further stratified as COVID-related or un-related as reported by the patient's clinical team.

Statistical analysis

Demographic, clinical characteristics and outcomes were summarised using frequencies and proportions for categorical variables and median and inter-quartile range (IQR) for continuous variables. We investigated associations between key baseline characteristics and the primary outcome of hospitalisation with supplemental oxygen using multivariable logistic regression. We derived adjusted odds ratios (AOR), 95% confidence intervals (CI) and two-sided p-values for the associations. Correlation between patients within countries was accounted for using robust standard errors in multivariable analyses(15). Model covariates were selected *a priori* based on evidence from previous studies and were checked for multicollinearity before inclusion in the models. Model assumptions were assessed graphically.

The primary multi-variable analysis included all patients aged ≥6 years, as ppFEV$_1$ measurements are not typically reported in CF registries in children <6 years of age. A secondary analysis was conducted for the non-transplanted patient cohort. Recognising post-transplant patients were likely to have a different lung disease process and medication history, this included additional variables; *Pseudomonas aeruginosa* infection status, BMI and CFTR modulator (CFTRm) use. The third planned fully adjusted multivariable analysis was not conducted for the outcome of admission to ICU due to low numbers of patients with this outcome.

Missing data were initially dealt with using clinical imputation rules then multiple imputation with chained equations (MICE) using fully conditional specification applied to all variables in the analysis models, and adjusted model estimates were approximated by combining Rubin's rules(16). More details on missing data analysis can be found in *Supplementary statement 1*.

We conducted an ad-hoc sensitivity analysis of the non-transplant model in US/UK patients only. In 2020 the highly effective Elex/Tez/Iva were more commonly available in these countries.

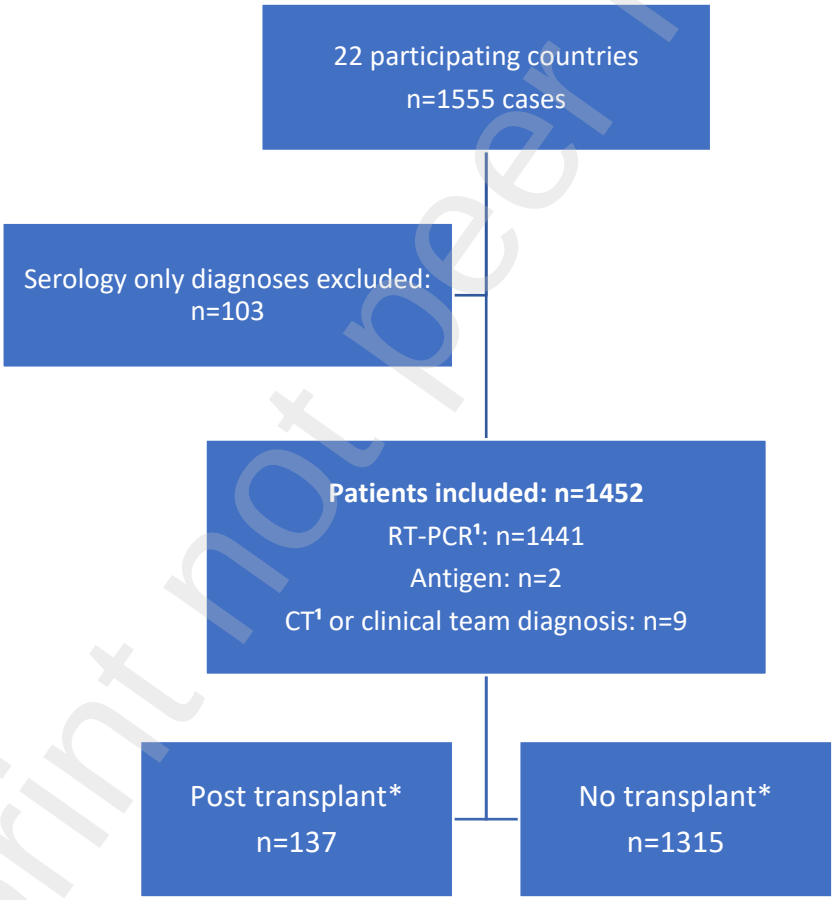
Study reporting and missing data analysis were guided by the STROBE(17) and STRATOS(18) frameworks. Data management and statistical analyses were done using Stata 15 and Stata 17. All tests were two-sided and $p<0.05$ was considered statistically significant.

Results

Participants

Twenty-two countries participated in this study, reporting 1555 people with CF diagnosed with SARS-CoV-2 infection between 1 February and 13 December 2020. These results suggest that at least 1.8% of the CF population in these countries was infected in this first year of the pandemic. 103 cases were excluded due to receiving a serology antibody only diagnosis rather than a test for acute SARS-CoV-2 infection, leaving 1,452 in the analysis cohort (*Figure 1*). Only 9 were included with a clinical or CT diagnosis from early in the pandemic, when RT-PCR testing was less available in some countries. The cases across countries ranged from zero cases in New Zealand to 751 in the USA.

Figure 1: Study flow diagram



**Any Solid organ transplant (n=122 lung transplant recipients). [1] RT-PCR=Reverse transcriptase polymerase chain reaction. CT=computed tomography.*

Descriptive data

Error! Reference source not found.A total of 1452 people with CF were included in the analysis (*Table 1*), four hundred and twenty-one (29%) were children (<18 years) and no cases of repeat infection were reported. More cases were reported during the final three months of the year than in the first 8 months of the study (882 vs. 570). The median age at SARS-CoV-2 infection was 24 years (IQR 16-33). **Error! Reference source not found.** The post-transplant group had a higher median age

than the non-transplant group (34 years vs. 23 years). Overall, 50.5% of the cohort were male, 72.9% of the cohort were white race and 82.5% had at least one copy of the F508del CFTR variant.

The median best ppFEV_1 pre-COVID-19 was 80%, with the distribution of lung function being comparable for non-transplant and post-transplant patients. The post-transplant cohort was small (n=137), some of the characteristics did however differ as shown in *Table 1*, of note for pancreatic insufficiency, BMI, CFRD and use of CFTRm drugs which are not widely prescribed post-transplant. Thirty-two individuals (11.1% of females aged >14 years in the cohort) were pregnant when they acquired the infection.

Table 1: Baseline demographic and clinical characteristics by transplant status

	Overall N=1452	**Non-transplant** N=1315	**Post-transplant** N=137
Sex; n (%)			
Male	733 (50.5)	659 (50.1)	74 (54.0)
Female	719 (49.5)	656 (49.9)	63 (46.0)
Age; Median (IQR)	24 (16-33)	23 (15-32)	34 (27-45)
Age; n (%)			
<18	421 (29.0)	415 (31.6)	6 (4.4)
18-39	806 (55.5)	722 (54.9)	84 (61.3)
≥40	225 (15.5)	178 (13.5)	47 (34.3)
Best ppFEV$_1$; Median (IQR)	79.9 (59.0-96.4)	80.0 (59.5-97.0)	78.0 (57.1-91.0)
Best ppFEV$_1$; n (%)			
<40%	102 (7.0)	89 (6.8)	13 (9.5)
40-70%	314 (21.6)	283 (21.5)	31 (22.6)
>70%	694 (47.8)	630 (47.9)	64 (46.7)
N/A (age <6 years)	90 (6.2)	89 (6.8)	1 (0.7)
Missing	252 (17.4)	224 (17.0)	28 (20.4)
BMI category[1]; n (%)			
Underweight	134 (9.2)	109 (8.3)	25 (18.2)
Normal	765 (52.7)	671 (51.0)	94 (68.6)
Overweight	294 (20.2)	280 (21.3)	14 (10.2)
Missing	259 (17.8)	255 (19.4)	4 (2.9)
Race; n (%)			
White	1059 (72.9)	973 (74.0)	86 (62.8)
Non-white	87	82 (6.2)	<6 (-)
Black	-	27 (2.1)	<6 (-)
Asian	-	17 (1.3)	<6 (-)
Any other race	-	38 (2.9)	<6 (-)
Missing	306 (21.1)	260 (19.8)	46 (33.6)
CFTR Genotype; n (%)			
Heterozygous F508del	620 (42.7)	565 (43.0)	55 (40.1)
Homozygous F508del	578 (39.8)	510 (38.8)	68 (49.6)
Other	252 (17.4)	238 (18.1)	14 (10.2)
Missing	2 (0.1)	2 (0.2)	0 (0.0)
CF-related diabetes; n (%)			
Yes	362 (24.9)	268 (20.4)	94 (68.6)
Missing	87 (6.0)	77 (5.9)	10 (7.3)
***P. aeruginosa* infection[2]; n (%)**			
Yes	655 (45.1)	600 (45.6)	55 (40.1)
Missing	96 (6.6)	52 (4.0)	44 (32.1)
Pancreatic insufficiency; n (%)			
Yes	1167 (80.4)	1037 (78.9)	130 (94.9)
Missing	39 (2.7)	34 (2.6)	5 (3.6)
Systemic Hypertension; n (%)			
Yes	77 (5.3)	37 (2.8)	40 (29.2)
Missing	283 (19.5)	255 (19.4)	28 (20.4)

	Overall	Non-transplant	Post-transplant
	N=1452	N=1315	N=137
CFTR modulators[3]; n (%)			
Any CFTR modulator	751 (51.7)	738 (56.1)	13 (9.5)
Iva or Elex/Tez/Iva	556 (38.3)	544 (41.4)	12 (8.8)
Lum/Iva or Tez/Iva	195 (13.4)	194 (14.8)	1 (0.7)
No CFTR modulator	685 (47.2)	563 (42.8)	122 (89.1)
Missing	16 (1.1)	14 (1.1)	2 (1.5)
Pregnant; n (%)			
Yes	32 (2.2)	32 (2.4)	0 (0.0)
Missing	353 (24.3)	328 (24.9)	25 (18.2)
Time of diagnosis			
Feb-May	198 (13.6)	161 (12.2)	37 (27.0)
June-Sept	372 (25.6)	351 (26.7)	21 (15.3)
Oct-Dec	882 (60.7)	803 (61.1)	79 (57.7)

Proportions are calculated from column totals (n/N). Where no 'Missing' row is included, variables are 100% complete. [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 year prior to SARS-CoV-2 diagnosis. [3] Using CFTR modulators at the time of SARS-CoV-2 diagnosis.
Iva=Ivacaftor
Elex/Tez/Iva=combination Elexacaftor/Tezacaftor/Ivacaftor
Lum/Iva=combination Lumacaftor/Ivacaftor
Tez/Iva=combination Tezacaftor/Ivacaftor
IQR=interquartile range
CFTR=cystic fibrosis transmembrane conductance regulator
BMI=body mass index
ppFEV$_1$=percent predicted forced expiratory volume in 1 second

Clinical Course

The presenting symptoms of SARS-CoV-2 infection are described in *Table 2*. Fever was the commonest symptom, present in 38% of people. A similar number (36%) reported increased cough. There were slight differences between the cohorts, notably for fatigue and fever. The proportion with fever and cough did not change across the age ranges (Supplementary table 2)

Three hundred and sixteen people were admitted to hospital in the overall cohort (*Table 2*) and 128 of them met the primary outcome of interest requirement for supplemental oxygen. Of these 316 there was a marked difference in the proportion admitted from the post-transplant group (58% vs 18%). Of note the indications for hospitalisation were not standardised, relying on the local physicians to determine need. Once hospitalised the post-transplant group were also more commonly admitted to ICU, required invasive ventilation, and received extracorporeal membrane oxygenation (ECMO). However, ECMO numbers were small with only 2 in each group. Similar proportions in each cohort received NIV and the primary outcome measure of supplemental oxygen after admission to hospital. 10 people died in each group following SARS-CoV-2 infection with 3 of these felt not to be related to SARS-CoV-2 as assessed by the treating physician.

Table 2: Infection management and disease course by transplant status

n (%)	Overall N=1452	Non-transplant N=1315	Post-transplant N=137
Hospitalisation			
No	1086 (74.8)	1030 (78.3)	56 (40.9)
Yes	316 (21.8)	236 (17.9)	80 (58.4)
Missing	50 (3.4)	49 (3.7)	1 (0.7)
Hospitalisation with supplemental oxygen[1]			
No	1241 (85.5)	1145 (87.1)	96 (70.1)
Yes	128 (8.8)	98 (7.5)	30 (21.9)
Missing	83 (5.7)	72 (5.5)	11 (8.0)
Intensive care unit admission			
No	1373 (94.6)	1263 (96.0)	110 (80.3)
Yes	46 (3.2)	27 (2.1)	19 (13.9)
Missing	33 (2.3)	25 (1.9)	8 (5.8)
Non-invasive ventilation			
No	1361 (93.7)	1242 (94.4)	119 (86.9)
Yes	29 (2.0)	21 (1.6)	8 (5.8)
Missing	62 (4.3)	52 (4.0)	10 (7.3)
Invasive Mechanical ventilation			
No	1363 (93.9)	1245 (94.7)	118 (86.1)
Yes	20 (1.4)	11 (0.8)	9 (6.6)
Missing	69 (4.8)	59 (4.5)	10 (7.3)
ECMO			
No	1357 (93.5)	1233 (93.8)	124 (90.5)
Yes	4 (0.3)	2 (0.2)	2 (1.5)
Missing	91 (6.3)	80 (6.1)	11 (8.0)
Vital status[2]			
Alive	1432 (98.6)	1305 (99.2)	127 (92.7)
Died (any cause)	20 (1.4)	10 (0.8)	10 (7.3)
Died (COVID-19)	17 (1.2)	9 (0.7)	8 (5.8)
Symptoms[3]			
Fever	558 (38.4)	489 (37.2)	69 (50.4)
Myalgia (joint pain)	141 (9.7)	117 (8.9)	24 (17.5)
Dyspnea (shortness of breath)	266 (18.3)	229 (17.4)	37 (27.0)
Increased cough	522 (36.0)	480 (36.5)	42 (30.7)
Fatigue	234 (16.1)	199 (15.1)	35 (25.5)
Other	467 (32.2)	427 (32.5)	40 (29.2)
Any symptoms	1082 (74.5)	968 (73.6)	114 (83.2)
Missing	38 (2.6)	34 (2.6)	4 (2.9)

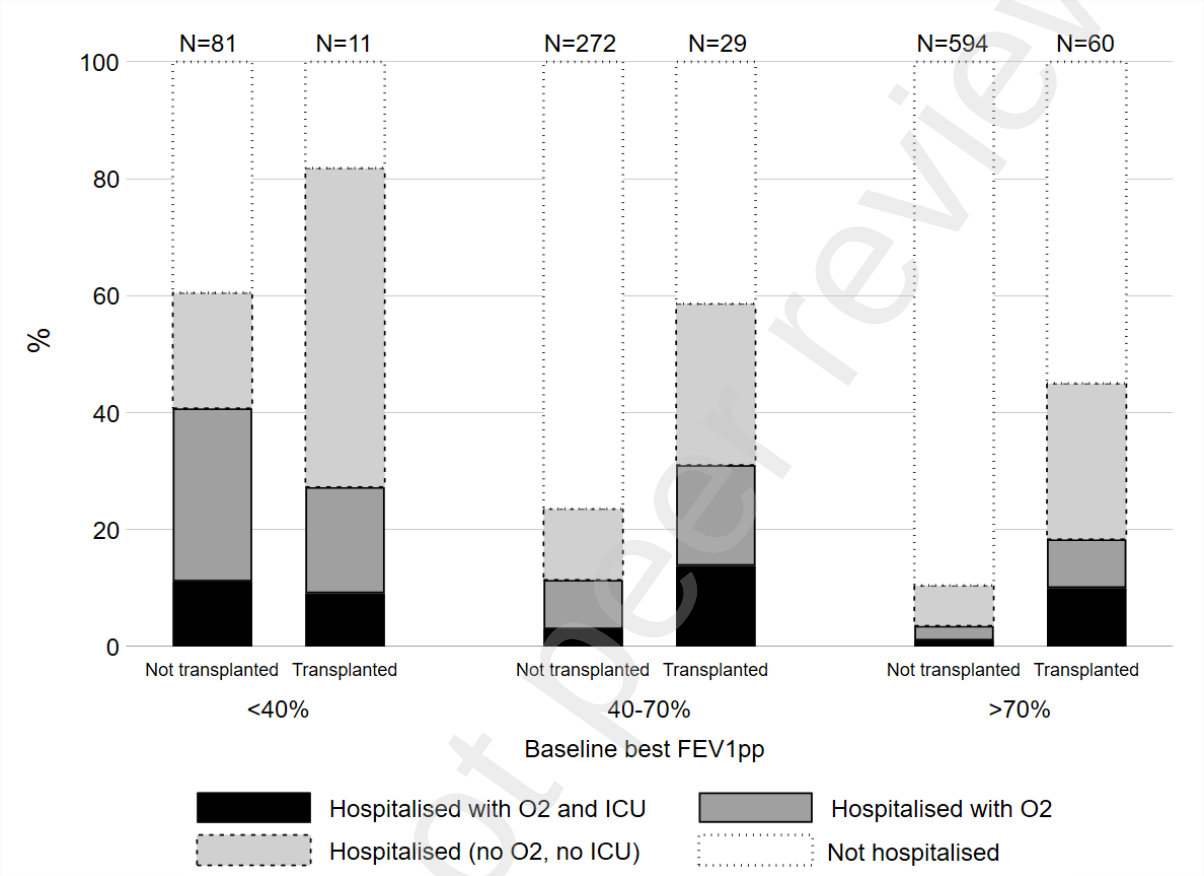
Proportions are calculated from column totals (n/N)

[1] New or additional supplemental oxygen [2] As of 15th January 2021 [3] Symptom categories are not mutually exclusive, with patients able to experience >1

ECMO=Extracorporeal membrane oxygenation

Irrespective of transplant status, higher proportions of people with lower baseline lung function were hospitalised. The distribution for the use of supplemental oxygen and ICU admission within hospitalised patients by lung function and transplant status is displayed in *Figure 2*. Rates of hospital admission, with supplemental oxygen and intensive care admission, also increased with older age when looking at the non-transplant cohort (*Supplementary Figure 1*).

Figure 2: Disease course by transplant status and baseline Best ppFEV$_1$



People >6 years, with non-missing outcome and baseline best ppFEV$_1$ data are included in this graph (N=1047). Total non-missing for each group are represented as bar labels – e.g., N=81 non-transplanted patients with <40% ppFEV$_1$ had non-missing outcome values. Outcomes are coded as mutually exclusive – note that this differs from how the data are presented in Tables 2-3.

The demographic and clinical characteristics by outcomes in the non-transplanted cohort are shown in *Table 3*. In the non-transplant cohort, 16.0% patients aged ≥40 years with non-missing outcome data were hospitalised with supplemental oxygen, compared with 4.3% aged <18 years. A higher proportion of people with baseline best ppFEV$_1$ <40% (39.5%) were also hospitalised with oxygen, than those with ppFEV$_1$ >70% (3.2%). Similarly, a higher proportion of people in the underweight BMI category were reported with the primary outcome – 22.1% compared with 8.4% of those with a normal BMI. Lower rates of hospitalisation with oxygen were observed in patients prescribed any CFTRm therapies (5.9%) compared with those with no modulators (10.6%).

Of the 236 that were hospitalised in the non-transplant group, 98 (42%) required supplemental oxygen, 27 (11.4%) were admitted to an intensive care unit, and 21 (8.9%) had NIV. Descriptive data for the whole cohort, including transplanted patients, is shown in the *Supplementary Table 3*. Of the 126 post-transplant patients with non-missing outcome data, 23.8% were hospitalised with

supplemental oxygen, compared with 7.9% of the non-transplanted patients. Similarly, a higher proportion of post-transplant patients (14.7%) were admitted to ICU following SARS-CoV-2 infection than non-transplanted patients (2.1%).

Table 3: Demographic and clinical characteristics by disease course (non-transplant cohort, N=1315)

	Hospitalisation with supplemental oxygen		**Hospitalisation**		**Intensive care unit**	
	N=1243		N=1266		N=1290	
	n/N	**%**	**n/N****	**%**	**n/N**	**%**
Sex; n (%)						
Male	51/619	8.2	115/632	18.2	16/645	2.5
Female	47/624	7.5	121/634	19.1	11/645	1.7
Age; n (%)						
<18	17/394	4.3	62/401	15.5	<6/408	-
18-39	54/680	7.9	127/696	18.2	12/706	1.7
≥40	27/169	16.0	47/169	27.8	10/176	5.7
Best FEV_1; n (%)						
<40%	32/81	39.5	51/83	61.4	9/87	10.3
40-70%	30/271	11.1	68/275	24.7	8/280	2.9
>70%	19/591	3.2	70/599	11.7	6/620	1
BMI category; n (%)						
Underweight	23/104	22.1	42/105	40.0	<6/108	-
Normal	52/624	8.3	126/637	19.8	14/657	2.1
Overweight	15/264	5.7	42/269	15.6	6/275	2.2
Race; n (%)						
White	58/951	6.1	153/972	15.7	21/951	2.2
Non-white	14/81	17.3	26/82	31.7	<6/81	-
Black	6/26	23.1	10/27	37.0	<6/26	-
Asian	0/17	0.0	4/17	23.5	0/17	0
Any other race	8/38	21.1	12/38	31.6	<6/38	-
Genotype; n (%)						
Heterozygous F508del	41/516	7.9	90/527	17.1	10/553	1.8
Homozygous F508del	33/500	6.6	91/510	17.8	12/500	2.4
Other	24/225	10.7	55/227	24.2	<6/235	-
CF-related diabetes; n (%)						
No	60/945	6.3	152/959	15.8	15/955	1.6
Yes	34/264	12.9	75/268	28.0	11/264	4.2
***P. aeruginosa* infection; n (%)**						
No	32/636	5.0	88/643	13.7	11/656	1.7
Yes	64/565	11.3	141/576	24.5	15/587	2.6

	Hospitalisation with supplemental oxygen		Hospitalisation		Intensive care unit	
	N=1243		N=1266		N=1290	
	n/N	**%**	**n/N****	**%**	**n/N**	**%**
Pancreatic insufficiency; n (%)						
No	11/225	4.9	26/227	11.5	3/243	1.2
Yes	87/989	8.8	204/1005	20.3	24/1018	2.4
CFTR modulators; n (%)						
Any CFTR modulator	42/713	5.9	105/726	14.5	14/725	1.9
Iva or Elex/Tez/Iva	27/528	5.1	68/539	12.6	11/533	2.1
Lum/Iva or Tez/Iva	15/185	8.1	37/187	19.8	3/192	1.6
No modulator	55/520	10.6	124/527	23.5	13/555	2.3
Time of diagnosis; n (%)						
Feb-May	30/157	19.1	69/161	42.9	9/157	5.7
June-Sept	27/340	7.9	60/348	17.2	9/343	2.6
Oct-Dec	41/746	5.5	107/757	14.1	9/790	1.1

Column row totals represent non missing data for the column outcome. Row proportions are calculated from the total non-missing in each outcome (See Table 1 for missing data). CFTR=cystic fibrosis transmembrane conductance regulator. FEV1=forced expiratory volume in 1 second, BMI=body mass index. Iva=ivacaftor, elex=elexacaftor, tez=tezacaftor

Multivariable analysis

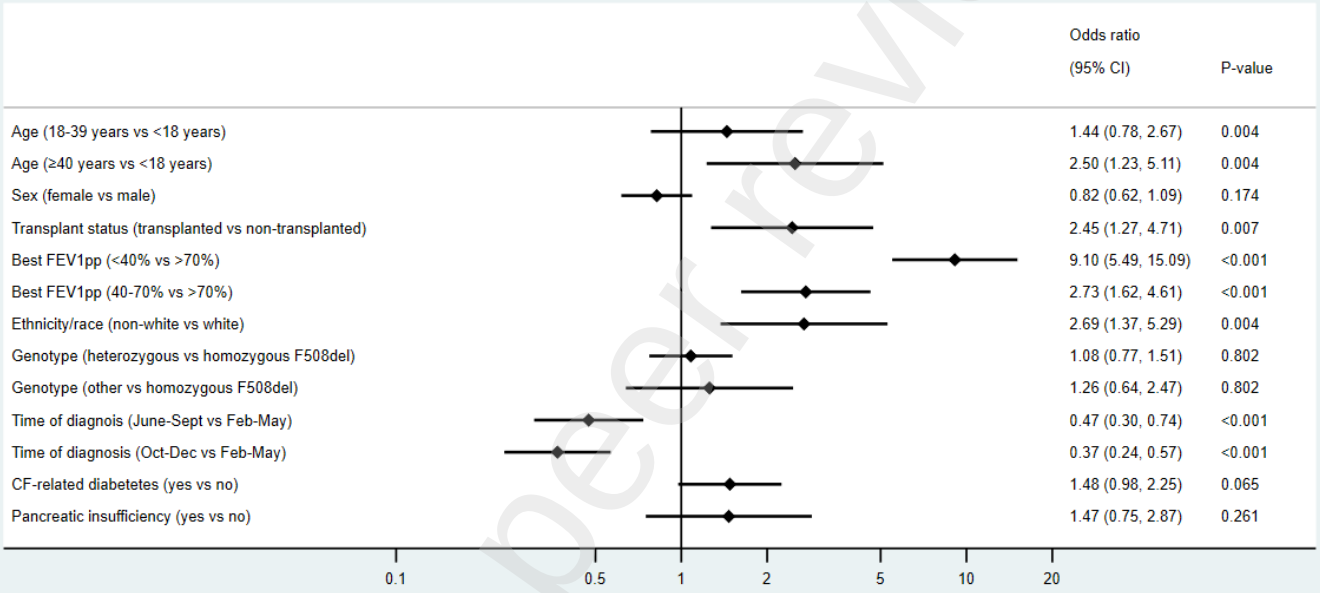
For those over 6 years of age the results of the primary multivariable analysis for hospitalisation with new or additional supplemental oxygen across the whole cohort of people with CF diagnosed with SARS-CoV-2 is shown in *Figure 3* (n=1362). Having a pre-pandemic baseline best $ppFEV_1$ <40% compared with >70% was associated with a 9-times higher risk of being hospitalised with oxygen (AOR 9.10 95%CI 5.49-15.09 p<0.001). Other factors associated with the main outcome of hospitalisation with supplemental oxygen are being of an older age (AOR 2.50 95%CI 1.23-5.11 p=0.004), having received a transplant (AOR 2.45 95%CI 1.27-4.71 p=0.007), being of non-white race (AOR 2.69 95%CI 1.37-5.29 p=0.004), and a diagnosis earlier in the pandemic (Supplementary table 4).

Multivariable analysis of the 1315 non-transplant patients included the additional variables of BMI, *Pseudomonas aeruginosa* infection status and use of a CFTRm therapy (*Figure 4*). The associations observed in the primary analysis remained, with additional factors showing evidence of independent associations including underweight BMI (AOR 2.07 95%CI 1.33-3.22 p=0.007), CFRD (AOR 1.56 95%CI 1.01-2.40 p=0.045) and *Pseudomonas aeruginosa* infection (AOR 1.41 95%CI 1.00-1.99 p=0.049). CFTRm use showed a negative association with the outcome, specifically for highly effective modulators compared with no modulators (AOR 0.43 95%CI 0.31-0.60 p<0.001) (Supplementary table 5). A limited multivariable analysis was performed for the outcome of intensive care admission, because of the small number admitted to ICU (n=46) a limited number of variables were included in the analysis the age and sex adjusted odds ratios are shown in *Supplementary table 6*, with female

showing a protective effect AOR 0.58 (0.42-0.81) and a transplant AOR of 6.13 (3.05-12.34). Data for the non-transplant cohort are shown in *Supplementary table 7* for information.

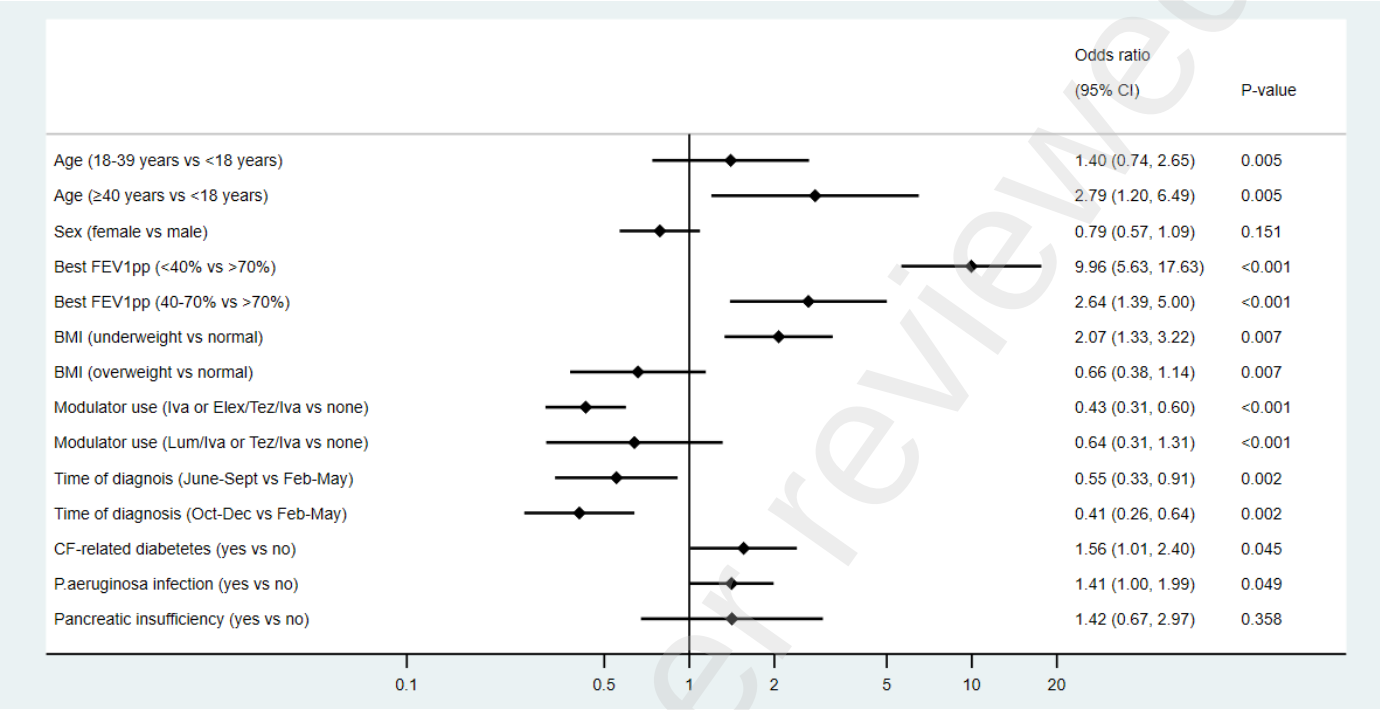
The sensitivity analysis in the non-transplant cohort, with patients from the US and UK only, showed that the evidence of effect of highly effective CFTRm therapies remained, showing a protective effect with a 59% reduction in risk of the primary outcome compared with no modulators (AOR 0.41 95%CI 0.18-0.90 p=0.079) (Supplementary Table 8).

Figure 3: Multivariable analysis for hospitalisation with supplemental oxygen in all patients (n=1362, m10)



All analyses are adjusted for clustering on country using robust standard errors. Excluding people aged <6 years as $ppFEV_1$ measurements are not recommended in this age group. p values shown represent the overall p values for the variable and are not associated with the level-to-level comparisons within these variables, which are represented by the 95% CIs. CI=Confidence interval $ppFEV_1$=forced expiratory volume in 1 second percent predicted, BMI=body mass index, Iva=ivacaftor, elex=elexacaftor, tez=tezacaftor m10=multiple imputed dataset with 10 iterations.

Figure 4: Multivariable analysis for hospitalisation with supplemental oxygen in the non-transplant cohort (N=1226, *m*=10)



All analyses are adjusted for clustering on country using robust standard errors. Excluding people aged <6 years as ppFEV$_1$ measurements are not recommended in this age group. p values shown represent the overall p values for the variable and are not associated with the level-to-level comparisons within these variables, which are represented by the 95% CIs. CI=Confidence interval ppFEV$_1$=forced expiratory volume in 1 second percent predicted, BMI=body mass index, Iva=ivacaftor, elex=elexacaftor, tez=tezacaftor m10=multiple imputed dataset with 10 iterations.

Discussion

This global study of 1452 individuals represents the largest cohort of people with CF in an analysis for the impact of SARS-CoV-2 infection prior to the licensing of SARS-CoV-2 vaccines. We used a composite end point of hospitalisation with additional oxygen supplementation to indicate severe infection. Hospitalisation alone can be a poor discriminator in a population where, due to established underlying disease factors, approximately 40% will be admitted to hospital for IV antibiotic therapy at least once each year(2).

The study has confirmed that transplant remains an independent risk factor for more severe SARS-CoV-2. The study included 137 people with CF who had received a solid organ transplant (122 lung transplants). They showed a greater proportion requiring hospitalisation, supplemental oxygen, being admitted to ICU, requiring invasive ventilation, and dying than in the non-transplant population.

Poor lung function, especially in those with ppFEV$_1$ <40 has emerged as key potential risk factor for severe SARS-CoV-2. Our results show this is the case in both non-transplant and post-transplant groups. When looking at the post-transplant group in more detail, the proportions across the three lung function categories are similar to those in the non-transplant group (*Figure 2*). This suggests that severe post-transplant lung disease, usually due to chronic lung allograft dysfunction, is a risk factor independent of immune suppression in this group.

Older age is known to be a risk factor for admission and death with SARS-CoV-2 in the general population. The median age at admission to hospital for this cohort was 28 years, with those having been transplanted slightly older (36 years) as would be expected given CF disease progression over time leads to transplant. When removing the post-transplant group from the analysis, older age remained an independent risk factor for severe disease. For both groups this was much younger than reported across the general population.

An important new finding of this study that has not previously been reported is that being of non-white race appears to be associated with a higher risk of severe infection for people with CF. This is in-line with results for the general population, which may be associated with socioeconomic or genetic factors as well as pathophysiological differences(19). It is worth noting this was a significant finding despite our study classifying people of Hispanic race/ethnicity as white. Evidence from the USA confirm Hispanics populations have worse outcomes with SARS-CoV-2(20).

Prescription of CFTRm therapy, especially so-called 'highly effective modulators' ivacaftor and elaxacaftor/tezacaftor/ivacaftor, was shown to have a protective effect against severe SARS-CoV-2 infection in non-transplanted patients. During the period of this study the modulator Elex/Tez/Iva was only widely available for prescription in the USA and UK, these also were also two of the countries with the highest rates of SARS-CoV-2 infection per capita in 2020(21). The robust standard error analysis method should have accounted for any clustering for example within countries however a sensitivity analysis on cases in only the two countries with highly effective CFTRm available provided further evidence that the association between highly effective modulators and outcome remained and confirmed it was not just an effect of different health care systems in these countries (*Supplementary table 5*). The use of CFTRm may also have impacted the finding that genotype group did not appear to be a risk factor, although a recent paper shows that CFTR function which is related to genotype correlates well with lung disease and other clinical features(22).

In the general population the risk of having SARS-CoV-2 whilst pregnant is a concern with high numbers having severe infection and what appears to be worse outcomes(23). Our study included 32 people with CF who were pregnant at the time of SARS-CoV-2 infection, no deaths were reported in this group, although small numbers prevent analysis for association with more severe disease course in this group.

Hospitalisation alone and hospitalisation with additional supplemental oxygen occurred at higher rates across the entire cohort during first three months of the pandemic. This is likely to be linked to the evolution of testing strategies as the pandemic progressed, in the early phases many countries were unable to test for suspected cases in the community meaning only those hospitalised will have been tested. Later in the pandemic, more robust testing regimens will have resulted in higher numbers of mild cases being definitively diagnosed with a positive RT-PCR in the community. There may also have been an evolution of knowledge about the effects of SARS-CoV-2 that meant that people with CF and infection were not automatically admitted if infection appeared mild.

CF-related diabetes was significantly associated with severe SARS-CoV-2 infection in the multivariate analysis of the non-transplant group. Similarly, *Pseudomonas aeruginosa* was associated with severe infection in the non-transplant group. Unlike SARS-CoV-2 in the general population, female sex does not appear to have a protective effect in the CF cohort. This may be related to females with CF tending to have poorer health outcomes in the first place(24).

In the multivariable analysis of the non-transplant group only, being underweight is associated with more severe infection. Being overweight may have a protective effect, in contrast to the linear increase in risk of hospital admission starting from BMI > 23 kg/m^2 observed in a large cohort of 6.9

million UK adults(25). However, given people with CF are often only mildly overweight, this finding is in line with current nutritional guidelines, which recommend BMI values above 23 kg/m^2 for male patients and above 22 kg/m^2 for female patients(26).

Strengths and Limitations

This study has the strength of including a very diverse range of countries across the globe, all with very different healthcare systems and different populations united by a common pandemic. The data collection proforma was agreed by an expert group and considered to be achievable and relevant for this patient population.

SARS-CoV-2 infection continues to be a rapidly evolving global situation with participating countries at different phases of the pandemic. Different countries have had different availability for testing at different stages. Many countries, such as the UK, had limited testing for SARS-CoV-2 in people in the first few months of the pandemic. Whilst people with CF are likely to be more closely clinically monitored than the general population, it is still likely that testing strategies varying over time and between countries means the overall CF population prevalence of 1.8% may be an under-estimate with the true denominator of people with CF who have been exposed and contracted SARS-CoV-2 in the community still not known. However, this study is not focused upon the total number or proportions hospitalised, but rather the risk factors for severe infection. While varying availability of testing was adjusted for in the multivariable analysis by using the time of diagnosis of a positive result, this risk of ascertainment bias should still be noted.

Whilst adjustments were made and sensitivity analysis conducted to account for differences between countries, the large proportion of cases coming from a small number of countries should be noted. Countries with larger CF populations, and higher absolute numbers of SARS-CoV-2 cases amongst them, also tend to have access to advanced healthcare systems, including CFTRm therapy and lung transplantation.

An argument for using admission to intensive care or invasive ventilation as markers for truly severe SARS-CoV-2 infection could be made. But with only 46 admitted to ICU within the 1432 reported cases the numbers are not high enough to do a meaningful multivariable analysis with this as the dependent variable. It is also not clear whether there were any barriers for admission to Intensive Care in this cohort but with predictive survival for individuals with severe lung disease (ppFEV <30%) being > 5 years we are hopeful that individuals with CF were admitted when appropriate(27).

This study is large but missing data must be noted as a limitation. This was addressed with modern techniques to impute the data for modelling purposes. Data was collected for acute treatment of SARS-CoV-2, however these have not been reported due to large amounts of missing data for IV antibiotics (47.4% missing), oral antibiotics (49.2% missing) and steroids (66.9% missing).

Interpretation

The disease course of SARS-CoV-2 amongst people with CF is varied and can be mild or even asymptomatic. However, the outcomes can be severe, resulting in hospitalisation, intensive care admission or even death in a small number of cases. People who are over 40 years old, have advanced lung disease (ppFEV$_1$ <40), or have received a solid-organ transplant are at higher risk of severe infection requiring hospitalisation and new or additional supplemental oxygen. People with CF should continue to follow guidance from medical experts to guard against infection, including ensuring that they and their families receive and keep up-to-date with COVID-19 vaccination.

The finding that highly effective modulator therapy may be protective against severe disease and hospitalisation caused by SARS-Cov-2 supports the policy that all people with CF who are likely to benefit should have immediate access to these medicines.

Generalisability

The risk for severe disease in those with low lung function in both the post-transplant and non-transplant group, who effectively have different underlying mechanisms for their lung disease, means that an absolute reduction in lung volume is likely to be a risk factor rather than just the mechanism behind the lung disease.

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Supplemental materials

Supplementary table 1*: Background CF population coverage*
CF population estimates drawn from National Registry reports where available. Accuracy of estimates and SARS-CoV-2 testing strategies and coverage vary by country

Country	Estimated CF population (year of estimate)
Argentina	-
Armenia	-
Australia	3538 (2020)
Belgium	1362 (2019)
Brazil	6189 (2021)
Canada	4344 (2019)
Chile	-
France	7280 (2019)
Germany	6669 (2020)
Ireland	1307 (2019)
Italy	5801 (2020)
Kazakhstan	-
Netherlands	1563 (2020)
New Zealand	530
Peru	-
Russia	3169 (2019)
South Africa	-
Spain	2536 (2019)
Sweden	704 (2019)
Switzerland	1028 (2020)
UK	10655 (2019)
USA	31411(2020)
Total	88086

Supplementary statement 1 *– Missing data analysis*

Missing data were handled initially using *a priori* clinical imputation rules. Our expert clinical group concluded that transplant status is well enough reported in all countries, that a missing value could be assumed as non-transplant. In the US dataset, it was assumed that a missing value for hospitalisation was “No” (not hospitalised). A clinical carryover rule was applied to treatment outcomes (ICU admission, supplemental oxygen, non-invasive ventilation, mechanical ventilation, ECMO), whereby if hospitalisation variable was “No”, the subsequent treatment outcomes were imputed as “No” if missing. We report missing data for variables of interest in Table 1-2 after the implementation of these rules.

For multivariable analyses, remaining missing data were handled using multiple imputation (MI). It was concluded that, due to the high number of incomplete cases across analysis variables (52%) and on the assumption that data in multiple variables and outcomes were not missing completely at random, complete-case analysis may have been biased and imprecise, and that MI was appropriate. Multiple imputation with chained equations (MICE) was conducted using fully conditional specification applied to all variables in the analysis models (CFRD, genotype, race, FEV_1, BMI, *P. aeruginosa* infection, pancreatic insufficiency, modulator use, hospitalisation, supplemental oxygen, ICU admission, age, sex, transplant status, time of diagnosis, country) and auxiliary variables (any symptoms, non-invasive ventilation, mechanical ventilation). BMI and FEV_1 were included as linear continuous variables and imputed using predictive mean matching drawing from 5 nearest neighbours to avoid imputing impossible values. Categorical variables were imputed using logistic or multinomial logistic regression as appropriate. 10 datasets were imputed with a burn-in of 10 iterations. MI was run using the *mi impute chained* command in Stata 15. The *augment* option was added to avoid perfect prediction in the logistic and multinomial regression models. Convergence issues were assessed by examining the MI trace file, reshaping the imputed dataset to obtain means and standard deviations of variables in each iteration, and checking for convergence using a *tsline* plot.

Supplementary table 2*: Disease course and outcomes by Age, Symptoms and pregnancy status*

n (%)	**Overall** N=1452	**Age <6 years** N=90	**Age <18 years** N=421	**Age ≥18 years** N=1031	**Asymptomatic[4]** N=332	**Symptomatic[4]** N=1082	**Pregnant** N=32
Symptoms[1]							
Fever	558 (38.4)	33 (36.7)	158 (37.5)	400 (38.8)	0 (0.0)	558 (51.6)	7 (21.9)
Myalgia (joint pain)	141 (9.7)	1 (1.1)	17 (4.0)	124 (12.0)	0 (0.0)	141 (13.0)	1 (3.1)
Dyspnea (shortness of breath)	266 (18.3)	4 (4.4)	37 (8.8)	229 (22.2)	0 (0.0)	266 (24.6)	9 (28.1)
Altered cough	522 (36.0)	34 (37.8)	145 (34.4)	377 (36.6)	0 (0.0)	522 (48.2)	9 (28.1)
Fatigue	234 (16.1)	10 (11.1)	47 (11.2)	187 (18.1)	0 (0.0)	234 (21.6)	5 (15.6)
Other	467 (32.2)	34 (37.8)	124 (29.5)	343 (33.3)	0 (0.0)	467 (43.2)	14 (43.8)
Any symptoms	1082 (74.5)	62 (68.9)	288 (68.4)	794 (77.0)	0 (0.0)	1082 (100.0)	24 (75.0)
Missing	38 (2.6)	2 (2.2)	11 (2.6)	27 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)
Hospitalisation							
No	1086 (74.8)	74 (82.2)	340 (80.8)	746 (72.4)	299 (90.1)	762 (70.4)	21 (65.6)
Yes	316 (21.8)	12 (13.3)	67 (15.9)	249 (24.2)	32 (9.6)	273 (25.2)	11 (34.4)
Missing	50 (3.4)	4 (4.4)	14 (3.3)	36 (3.5)	1 (0.3)	47 (4.3)	0 (0.0)
ICU admission							
No	1373 (94.6)	86 (95.6)	408 (96.9)	965 (93.6)	320 (96.4)	1028 (95.0)	27 (84.4)
Yes	46 (3.2)	<6	6 (1.4)	40 (3.9)	1 (0.3)	43 (4.0)	<6
Missing	33 (2.3)	3 (3.3)	7 (1.7)	26 (2.5)	11 (3.3)	11 (1.0)	3 (9.4)

n (%)	Overall N=1452	Age <6 years N=90	Age <18 years N=421	Age ≥18 years N=1031	Asymptomatic[4] N=332	Symptomatic[4] N=1082	Pregnant N=32
Supplemental oxygen[2]							
No	1264 (87.1)	84 (93.3)	393 (93.3)	871 (84.5)	317 (95.5)	921 (85.1)	25 (78.1)
Yes	129 (8.9)	<6	18 (4.3)	111 (10.8)	3 (0.9)	125 (11.6)	<6
Missing	59 (4.1)	3 (3.3)	10 (2.4)	49 (4.8)	12 (3.6)	36 (3.3)	<6
Hospitalisation with supplemental oxygen[2]							
No	1241 (85.5)	80 (88.9)	382 (90.7)	859 (83.3)	317 (95.5)	898 (83.0)	25 (78.1)
Yes	128 (8.8)	<6	18 (4.3)	110 (10.7)	3 (0.9)	124 (11.5)	<6
Missing	83 (5.7)	7 (7.8)	21 (5.0)	62 (6.0)	12 (3.6)	60 (5.5)	<6
Non-invasive ventilation							
No	1361 (93.7)	86 (95.6)	405 (96.2)	956 (92.7)	320 (96.4)	1015 (93.8)	29 (90.6)
Yes	29 (2.0)	<6	6 (1.4)	23 (2.2)	0 (0.0)	28 (2.6)	0 (0.0)
Missing	62 (4.3)	3 (3.3)	10 (2.4)	52 (5.0)	12 (3.6)	39 (3.6)	<6
Mechanical ventilation							
No	1363 (93.9)	86 (95.6)	409 (97.1)	954 (92.5)	319 (96.1)	1019 (94.2)	28 (87.5)
Yes	20 (1.4)	0 (0.0)	<6	19 (1.8)	1 (0.3)	17 (1.6)	<6
Missing	69 (4.8)	4 (4.4)	11 (2.6)	58 (5.6)	12 (3.6)	46 (4.3)	3 (9.4)
ECMO							
No	1357 (93.5)	82 (91.1)	397 (94.3)	960 (93.1)	320 (96.4)	1011 (93.4)	29 (90.6)
Yes	4 (0.3)	<6	<6	3 (0.3)	0 (0.0)	4 (0.4)	0 (0.0)
Missing	91 (6.3)	7 (7.8)	23 (5.5)	68 (6.6)	12 (3.6)	67 (6.2)	<6
Vital status[3]							
Not died	1432 (98.6)	90 (100.0)	418 (99.3)	1014 (98.4)	331 (99.7)	1065 (98.4)	32 (100.0)
Died (any cause)	20 (1.4)	0 (0.0)	3 (0.7)	17 (1.6)	1 (0.3)	17 (1.6)	0 (0.0)
Died (COVID-19)	17 (1.2)	0 (0.0)	1 (0.2)	16 (1.6)	1 (0.3)	14 (1.3)	0 (0.0)

Proportions are calculated from column totals (n/N) [1] Symptom categories are not mutually exclusive, with patients able to experience >1 [2] New or additional supplemental oxygen [3] As of 15th January 2021 [4] Patients with missing data for all symptom fields are excluded (N=38) ECMO=Extracorporeal membrane oxygenation

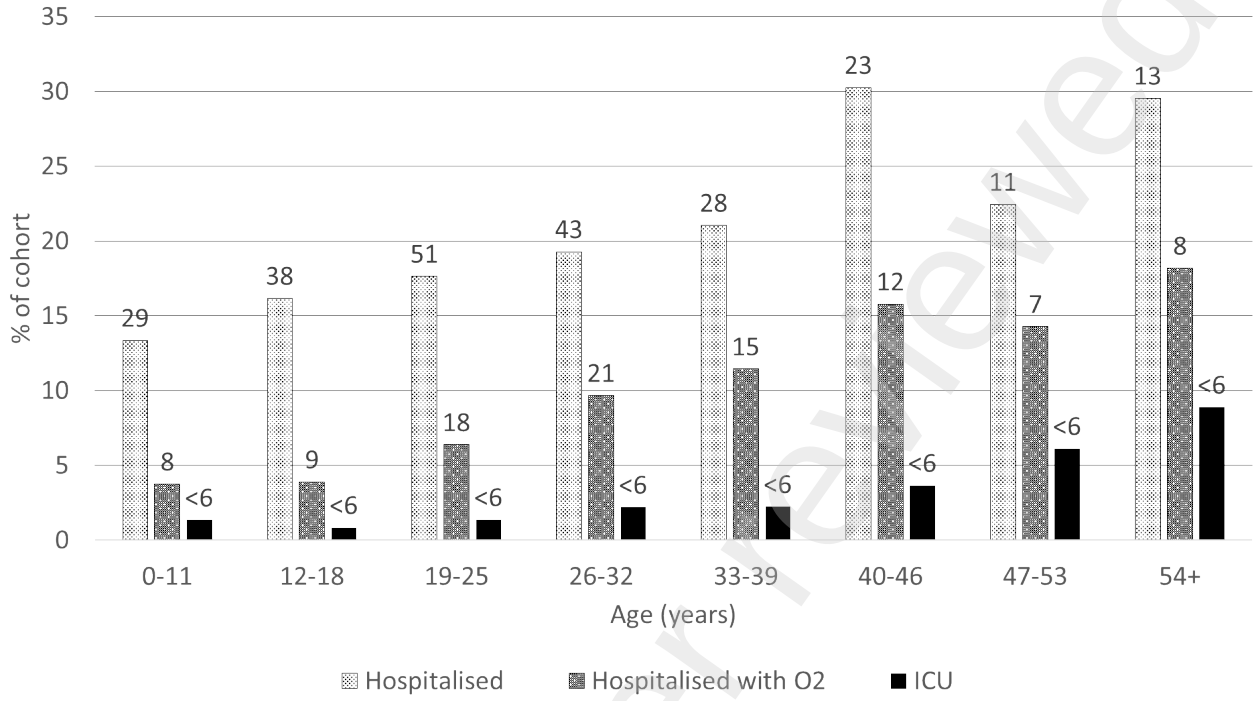
Supplementary table 3*: Demographic and clinical characteristics by disease course (all patients, including transplanted)*

	Hospitalisation with supplemental oxygen		Hospitalisation		Intensive care unit	
	N=1369		N=1402		N=1419	
	n/N	**%**	**n/N****	**%**	**n/N**	**%**
Transplant status; n (%)						
No	98/1243	7.9	236/1266	18.6	27/1290	2.1
Yes	30/126	23.8	80/136	58.8	19/129	14.7
Sex; n (%)						
	67/684	9.8	156/706	22.1	27/711	3.8
Female	61/685	8.9	160/696	23	19/708	2.7
Age; n (%)						
<18	18/400	4.5	67/407	16.5	6/414	1.4
18-39	70/756	9.3	174/779	22.3	22/784	2.8
≥40	40/213	18.8	75/216	34.7	18/221	8.1
Best FEV_1 pp; n (%)						
<40%	35/92	38	61/95	64.2	36434	10.1
40-70%	38/300	12.7	87/306	28.4	12/311	3.9
>70%	29/651	4.5	101/663	15.2	12/680	1.8
BMI category; n (%)						
Underweight	27/126	21.4	59/129	45.7	7/131	5.3
Normal	73/713	10.2	176/731	24.1	28/747	3.7
Overweight	18/275	6.5	52/283	18.4	8/287	2.8
Race; n (%)						
White	76/1030	7.4	200/1058	18.9	33/1030	3.2
Non-white	15/85	17.6	31/87	35.6	<6/85	-
Black	7/28	25	12/29	41.4	<6/28	-
Asian	0/18	0	<6/18	-	0/18	0
Any other race	8/39	20.5	14/40	35	<6/39	-
Genotype; n (%)						
Heterozygous F508del	53/566	9.4	124/581	21.3	17/606	2.8
Homozygous F508del	47/564	8.3	127/578	22	23/564	4.1
Other	28/237	11.8	65/241	27	6/247	2.4
CF-related diabetes; n (%)						
No	66/978	6.7	168/992	16.9	18/988	1.8
Yes	58/352	16.5	135/362	37.3	27/352	7.7
***P. aeruginosa* infection; n (%)**						
No	40/672	6	111/681	16.3	15/692	2.2
Yes	79/616	12.8	179/630	28.4	24/640	3.8

	Hospitalisation with supplemental oxygen		Hospitalisation		Intensive care unit	
	N=1369		N=1402		N=1419	
	n/N	**%**	**n/N****	**%**	**n/N**	**%**
Pancreatic insufficiency; n (%)						
No	13/227	5.7	28/229	12.2	3/245	1.2
Yes	115/1110	10.4	280/1134	24.7	43/1142	3.8
CFTR modulators; n (%)						
Any CFTR modulator	43/725	5.9	112/739	15.2	16/737	2.2
Iva or Elex/Tez/Iva	28/539	5.2	75/551	13.6	13/544	2.4
Lum/Iva or Tez/Iva	15/186	8.1	37/188	19.7	3/193	1.6
No modulator	84/632	13.3	197/648	30.4	30/670	4.5
Time of diagnosis; n (%)						
Feb-May	43/192	22.4	96/198	48.5	18/192	9.4
June-Sept	30/358	8.4	71/369	19.2	10/361	2.8
Oct-Dec	55/819	6.7	149/835	17.8	18/866	2.1

Row proportions are calculated from the total non-missing in each outcome. Where the values in a descriptive category do not add up to the overall column total this indicates incomplete data in the given descriptive (See Table 1 for missing data) CFTR=cystic fibrosis transmembrane conductance regulator FEV_1=forced expiratory volume in 1 second

Supplementary Figure 1: *Disease course by age in the non-transplant cohort (N=1315)*



Bar labels represent number of patients with each outcome in the specified age group. Outcomes are not mutually exclusive – ie. the people hospitalised with O2 and admitted to ICU in each age group are also contained in the "Hospitalised" bars.
O2 = new or additional supplemental oxygen therapy
ICU = intensive care unit admission

Supplementary table 4: - *Adjusted odds ratios for association with hospitalisation and supplemental oxygen (primary analysis, including transplanted patients)*

Covariate	OR (95% CI) adjusted for age and sex	OR (95% CI) adjusted for all covariates	p-value
Main analysis (N=1362, m10)			
Age			
<18	1 (ref)	1 (ref)	
18-39	2.07 (1.23-3.51)	1.44 (0.78-2.67)	0.004
40 & over	4.48 (2.30-8.71)	2.50 (1.23-5.11)	
Sex			
Male	1 (ref)	1 (ref)	
Female	0.80 (0.60-1.07)	0.82 (0.62-1.09)	0.174
Post-transplant	2.78 (1.58-4.86)	2.45 (1.27-4.71)	0.007
Baseline best ppFEV$_1$			
<40	11.03 (6.69-18.19)	9.10 (5.49-15.09)	
40-70	2.91 (1.77-4.81)	2.73 (1.62-4.61)	<0.001
>70	1 (ref)	1 (ref)	
Race			
White	1 (ref)	1 (ref)	
Non-white	4.11 (2.22-7.61)	2.69 (1.37-5.29)	0.004
Genotype			
Homozygous F508del	1 (ref)	1 (ref)	
Heterozygous F508del	0.97 (0.74-1.28)	1.08 (0.77-1.51)	0.802
Other	1.38 (0.87-2.19)	1.26 (0.64-2.47)	
Time of diagnosis			
Feb-May	1 (ref)	1 (ref)	
June-Sept	0.38 (0.27-0.53)	0.47 (0.30-0.74)	<0.001
Oct-Dec	0.27 (0.18-0.41)	0.37 (0.24-0.57)	
CF-related diabetes	2.30 (1.53-3.46)	1.48 (0.98-2.25)	0.065
Pancreatic insufficiency	2.10 (1.21-3.65)	1.47 (0.75-2.87)	0.261

P-values represent fully adjusted estimates, and are for associations of entire variables rather than level-to-level comparisons which are represented by CIs. Note that these results are presented graphically in Figure 3*.*
m10=estimates derived from 10 imputed datasets

Supplementary table 5 - *Adjusted odds ratios for association with hospitalisation and supplemental oxygen (secondary analysis, non-transplant patients)*

Covariate	OR (95% CI) adjusted for age and sex	OR (95% CI) adjusted for all covariates	p-value
Non-transplant analysis (N=1,226*, m=10)			
Age			
<18	1 (ref)	1 (ref)	
18-39	1.84 (0.98-3.46)	1.40 (0.74-2.65)	0.005
>40	3.83 (1.97-7.44)	2.79 (1.20-6.49)	
Sex			
Male	1 (ref)	1 (ref)	
Female	0.81 (0.62-1.06)	0.79 (0.57-1.09)	0.151
Baseline best ppFEV$_1$			
<40	16.68 (10.41-26.73)	9.96 (5.63-17.63)	
40-70	3.73 (2.16-6.43)	2.64 (1.39-5.00)	<0.001
>70	1 (ref)	1 (ref)	
BMI			
Underweight	3.98 (2.87-5.52)	2.07 (1.33-3.22)	
Normal	1 (ref)	1 (ref)	0.007
Overweight	0.51 (0.34-0.76)	0.66 (0.38-1.14)	
CFTR modulator use			
Iva or Elex/Tez/Iva	0.46 (0.29-0.72)	0.43 (0.31-0.60)	
Lum/Iva or Tez/Iva	0.82 (0.35-1.92)	0.64 (0.31-1.31)	<0.001
No modulator	1 (ref)	1 (ref)	
Time of diagnosis			
Feb-May	1 (ref)	1 (ref)	
June-Sept	0.40 (0.26-0.62)	0.55 (0.33-0.91)	0.002
Oct-Dec	0.26 (0.18-0.39)	0.41 (0.26-0.64)	
CF-related diabetes	1.97 (1.31-2.94)	1.56 (1.01-2.40)	0.045
P. aeruginosa infection	2.07 (1.43-3.00)	1.41 (1.00-1.99)	0.049
Pancreatic insufficiency	2.07 (1.08-3.98)	1.42 (0.67-2.97)	0.358

P-values represent fully adjusted estimates, and are for associations of entire variables rather than level-to-level comparisons which are represented by CIs. Note that these results are presented graphically in Figure 4*.*
m10=estimates derived from 10 imputed datasets

Supplementary table 6 – *Age- and sex-adjusted odds ratios for association with intensive care unit admission (primary analysis, including transplanted patients)*

Covariate	OR (95% CI) adjusted for age and sex
Main analysis (N=1362, m10)	
Age	
<18	1 (ref)
18-39	1.97 (0.72-5.41)
>40	5.39 (2.20-13.17)
Sex	
Male	1 (ref)
Female	0.58 (0.42-0.81)
Post-transplant	6.13 (3.05-12.34)
Baseline Best ppFEV$_1$	
<40	4.41 (2.17-8.97)
40-70	1.74 (0.92-3.31)
>70	1 (ref)
Race	
White	1 (ref)
Non-white	2.15 (0.84-5.54)
Genotype	
Homozygous	1 (ref)
Heterozygous	0.53 (0.24-1.20)
Other	0.49 (0.23-1.07)
Time of diagnosis	
Feb-May	1 (ref)
June-Sept	0.37 (0.21-0.66)
Oct-Dec	0.23 (0.10-0.52)
CF-related diabetes	3.55 (2.23-5.66)
Pancreatic insufficiency	4.16 (1.44-12.05)

Estimates adjusted for all covariates and p-values are not presented due to low numbers of patients with this outcome.

Supplementary table 7: *Age- and sex-adjusted odds ratios for association with intensive care unit admission (non-transplant analysis)*

Covariate	OR (95% CI) adjusted for age and sex
Non-transplant analysis (N=1,226, m=10)	
Age	
<18	1 (ref)
18-39	1.46 (0.34-6.35)
>40	4.24 (1.20-14.94)
Sex	

Male	1 (ref)
Female	0.59 (0.33-1.04)
Baseline Best ppFEV$_1$	
<40	8.19 (4.28-15.66)
40-70	2.49 (0.91-6.77)
>70	1 (ref)
BMI	
Underweight	2.52 (0.94-6.71)
Normal	1 (ref)
Overweight	0.64 (0.30-1.36)
CFTR modulator use	
Iva or Elex/Tez/Iva	1.01 (0.53-1.92)
Lum/Iva or Tez/Iva	0.81 (0.22-2.96)
No modulator	1 (ref)
Time of diagnosis	
Feb-May	1 (ref)
June-Sept	0.52 (0.22-1.19)
Oct-Dec	0.20 (0.08-0.46)
CF-related diabetes	2.19 (1.20-4.01)
***P.aeruginosa* infection**	1.44 (0.83-2.51)
Pancreatic insufficiency	2.67 (0.90-7.93)

Estimates adjusted for all covariates and p-values are not presented due to low numbers of patients with this outcome.

Supplementary table 8 – *sensitivity analysis*

A sensitivity analysis of association with hospitalisation with supplemental oxygen in the non-transplant cohort in the UK/US cohort only. These two jurisdictions have national reimbursement of all CFTR modulator therapy during the data capture period. Together, they contributed 794 (60.4%) cases to the non-transplant group.

Covariate	OR (95% CI) adjusted for all covariates	P-value
Non-transplant analysis (N=794*, m=10)		
Age (years)		
<18	1 (ref)	
18-39	3.14 (0.72-13.58)	0.045
> 40	7.03 (1.28-38.52)	
Sex		
Male	1 (ref)	
Female	0.89 (0.46-1.74)	0.740
Best FEV_1 pp		
<40%	7.97 (2.93-21.67)	
40-70%	1.74 (0.66-4.57)	<0.001
>70%	1 (ref)	
BMI		
Underweight	1.86 (0.64-5.40)	0.256
Normal	1 (ref)	
Overweight	0.63 (0.27-1.49)	
CFTR modulator use		
Iva or Elex/Tez/Iva	0.41 (0.18-0.90)	
Lum/Iva or Tez/Iva	0.59 (0.21-1.63)	0.079
No modulator	1 (ref)	
Time of diagnosis		
Feb-May	1 (ref)	
June-Sept	0.56 (0.22-1.38)	0.141
Oct-Dec	0.42 (0.17-1.00)	
CF-related diabetes	1.93 (1.00-3.74)	0.051
***P. aeruginosa* infection**	1.30 (0.65-2.59)	0.454
Pancreatic insufficiency	3.56 (0.92-13.80)	0.066

**US and UK cases only included in this analysis. P-values represent fully adjusted estimates, and are for associations of entire variables rather than level-to-level comparisons which are represented by CIs.*

m10=estimates derived from 10 imputed datasets

COI Statement:

All authors declare no conflicts of interest in relationship to this work. Outside of this work the following authors declare payments or honoraria to them or their institution for a combination of lectures, presentations, educational events, advisory boards, steering groups, grants or consultancy fees: SC-Vertex, Chiesi, Profile, Zambon. RC- Vertex, P-RB – Astra-Zeneca, Boehringer Ingelheim, GSK, Insmed, Chiesi, Pfizer, Vertex, Zambon. I deM – Vertex,LN – Vertex, Boehringer,LVS-F – Vertex, AS - Vertex.

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