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Early View

Original research article

Factors for severe outcomes following SARS-CoV-2 infection in people with cystic fibrosis in Europe

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Factors for severe outcomes following SARS-CoV-2 infection in people with cystic fibrosis in Europe

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Take Home Message

In a European study of SARS-CoV-2 infection in 828 people with CF, those with moderate-severe lung disease, CF-related diabetes and lung transplant had poorer outcomes. People with CF, especially these groups, should shield in priority.

Abstract

Background: SARS-Co-V-2 infection in people with CF (pwCF) can lead to severe outcomes.

Methods: In this observational study, the European Cystic Fibrosis Society Patient Registry collected data on pwCF and SARS-CoV-2 infection to estimate incidence, describe clinical presentation and investigate factors associated with severe outcomes using multivariable analysis.

Results: Up to 31 December 2020, 26 countries reported information on 828 pwCF and SARS-CoV-2 infection. Incidence was 17.2 per 1000 pwCF (95% CI: 16.0-18.4). Median age was 24 years, 48.4% were male and 9.4% had lung transplants. SARS-CoV-2 incidence was higher in lung-transplanted (28.6 [95% CI: 22.7–35.5]) versus non-lung transplanted pwCF (16.6 [95% CI: 15.4–17.8]) (p=<0.001).

SARS-CoV-2 infection caused symptomatic illness in 75.7%. Factors associated with symptomatic SARS-CoV-2 infection were age >40 years, at least one F508del mutation, and pancreatic insufficiency.

Overall, 23.7% were admitted to hospital, 2.5% to intensive care. Regretfully 11 pwCF (1.4%) died. Hospitalisation, oxygen therapy, intensive care, respiratory support and death were 2-6-fold more frequent in lung-transplanted versus non-lung transplanted pwCF.

Factors associated with hospitalisation and oxygen therapy were lung transplantation, CF-related diabetes (CFRD), moderate or severe lung disease and azithromycin use (often considered a surrogate marker for *Pseudomonas aeruginosa* infection and poorer lung function).

Conclusion: SARS-CoV-2 infection yielded high morbidity and hospitalisation in pwCF. PwCF with forced expiratory volume in one second (FEV_1) <70% predicted, CFRD and those with lung transplants are at particular risk of more severe outcomes.

Keywords

Cystic fibrosis, SARS-CoV-2, risk factors, observational, Covid-19

1 Background

The novel coronavirus SARS-CoV-2 infected over 79 million people worldwide in 2020, causing 1.7 million deaths [1].

Given that viral infection can cause pulmonary exacerbations and hasten lung function decline [2-4], people with cystic fibrosis (pwCF) took early steps to protect themselves from infection by shielding [5, 6]. Nonetheless, adult and paediatric pwCF have been infected [7-9].

We recently assessed the incidence of SARS-CoV-2 infection in a cohort of 130 pwCF in Europe up to the 30 June 2020 [7]. Other national and global studies have also assessed incidence and outcomes of SARS-CoV-2 infection in pwCF during the first wave of the pandemic [8, 10-12]. Lung transplanted pwCF appear to have worse outcomes than those without lung transplant. However robust multivariable data are still lacking regarding risk factors, as well as up to date incidence estimates.

Here we expand our previously described cohort [7] to include European pwCF who were diagnosed with SARS-CoV-2 infection up to 31 December 2020. In this cohort of 828 pwCF, we update SARS-CoV-2 incidence, and provide the first large, detailed analysis of clinical presentation (including individual symptoms) and identification of risk factors associated with poorer outcomes.

2 Methods

2.1 Study design

The methodology of this prospective observational study has been previously described in a paper presenting data collected between 01 February 2020 and 30 June 2020 [7]. Briefly, data regarding pwCF with PCR-confirmed SARS-CoV-2 infection were collected from CF centres participating in the European Cystic Fibrosis Society Patient Registry (ECFSPR). Cases diagnosed by CT scan, serology or antigen test without PCR confirmation were excluded. Data were reported directly to ECFSPR using a standardized case report form, except for Belgium, France, Germany and the UK who contributed data via their national registries. Two data sources were reported for Italy (national registry and the Italian CF society), with no double cases reported.

We collected data about demographics, pre-infection CF characteristics (latest data available, collected within 12 to 18 months before infection depending on the national data collection strategy) and information about SARS-CoV-2 infection regarding diagnosis, symptoms, complications, treatments and outcomes. Where appropriate, variables were defined according to ECFSPR standards (http://www.ecfs.eu/projects/ecfs-patient-registry/Variables-Definitions). Percent predicted forced expiratory volume in one second (ppFEV1) is referred to as mild (>70), moderate (>40-70), or severe (≤40) lung disease [13].

Each participating centre or national registry has ethical approval and patients' informed consent for data collection and ECFSPR participation, including consent that data may be used for future research.

2.2 Definitions of symptoms and outcomes

A pwCF was defined as symptomatic if they reported at least one symptom of SARS-CoV-2 infection. Symptoms were categorised as general, pulmonary, gastrointestinal or ear, nose and throat (ENT) and eye, (see Table 1). Outcomes were hospitalisation, intensive care, oxygen therapy, respiratory support and death (see Table 1).

2.3 Statistics

Results are presented for all pwCF and by lung transplant status. Demographics and pre-infection CF characteristics and treatments are presented using descriptive statistics. Categorical variables are described as counts and percentages and continuous variables as median and interquartile range. Fisher exact test was used to compare the percentage of categorical variables between groups and Wilcoxon test was used to compare the median on continuous variables between groups.

The denominator for incidence was the ECFSPR population from 2018 [14] (2017 for France [15]). We evaluated the association of demographic and pre-infection clinical characteristics of pwCF with the symptoms and outcome of SARS-CoV-2 infection. Mixed effects univariable logistic regression analyses considered SARS-CoV-2 symptoms and outcomes as response variable and the characteristics of pwCF as explanatory variable (retaining variables with <30% missing data). A country random effect accounted for the effect of health systems. Odds ratios (OR), with 95% confidence intervals (CI) and p-values were calculated.

Variables with <5% missing data were included in multivariable logistic regression models to identify independent predictors of symptoms and outcomes. Moreover, models were only fitted when the number of events in the response variable was ≥5 times the number of predictor variables [16]. Adjusted OR, with 95% CI and p-values were calculated. Data analysis was performed by ECFSPR statisticians, using SAS 9.4 and R 4.0.3 with the additional package geepack.

3 Results

3.1 Incidence

Of the 38 ECFSPR countries, 37 contributed information about SARS-CoV-2 infection in pwCF (**Figure 1**).

SARS-CoV-2 infections occurred in two distinct waves, the first in March and April 2020 with a second larger wave from October to December 2020. The second wave was ongoing at the time of data cut-off (

Figure 2). As per our previous report, incidence varied widely by country (

Figure 3, *Supplementary Table 1*).

Overall, 828 PCR-confirmed cases were reported from 26 countries, yielding an incidence of 17.2 per 1000 pwCF (95% CI: 16.0-18.4) (**Table 2**). Incidence was significantly higher in lung-

transplanted pwCF (28.6 [95% CI: 22.7–35.5]) versus non-lung transplanted pwCF (16.6 [95% CI: 15.4–17.8]) ($p<0.001$).

Incidence increased along with age group (Fisher exact test; $p<0.001$) and was notably higher in all adult age groups compared to paediatric age groups. Similar trends were observed for non-lung transplanted pwCF. In lung-transplanted pwCF, incidence did not vary notably between the age groups spanning 18-49 years; younger and older age groups had too few cases (<5) to allow comparison.

3.2 Demographics and CF characteristics

Of the 828 cases, 48.4% were male with a median age of 24 years (**Table 3**). Most pwCF had normal body mass index (BMI) (90.6%), pancreatic insufficiency (80.6%), and mild lung disease (59.9%). 26.1% had CF-related diabetes (CFRD) and 26.6% had chronic liver disease. Pre-infection medication use was common, and as expected for pwCF (**Table 3**). The most frequent pulmonary infections were *Staphylococcus aureus* (57.7%) and *Pseudomonas aeruginosa* (43.4%).

Compared to non-lung transplanted pwCF (n=750), lung transplanted pwCF (n=78) were older and more frequently F508del homozygous. They had higher rates of pancreatic insufficiency, CFRD, systemic arterial hypertension. Concomitant medications also differed, due to different indications and medical needs.

3.3 Symptoms and outcomes of SARS-CoV-2 infection

SARS-CoV-2 infection gave rise to symptomatic illness in 75.7% of pwCF (81.7% in lung-transplanted pwCF versus 75.1% in non-lung transplanted). Symptoms were most commonly general (64.8%), pulmonary (54.0%) and ENT & eyes (34.9%). The most common individual symptoms were fever (43.6%), increased cough (43.2%), fatigue (34.2%), myalgia/arthralgia (22.4%) and pulmonary exacerbation (21.2%) (**Table 1**).

Lung-transplanted pwCF had notably different rates of specific symptoms, with more frequent dyspnoea and respiratory failure and less frequent increased sputum and pulmonary exacerbation.

Of the 828 cases, 11.7% needed extra oxygen and 3.9% needed respiratory support, 23.7% were admitted to hospital and 2.5% to intensive care. Regretfully, 11 pwCF (1.4%) died. The case fatality rate was 1.4% (95% CI: 0.7-2.4). Demographic and baseline CF characteristics for the 11 pwCF who died are presented in *Supplementary Table 2*.

Oxygen therapy, respiratory support and hospitalization were >2-fold more common in lung transplanted pwCF versus non-lung transplanted; similarly, intensive care admission and death were 6-fold more common. In hospitalized patients, intensive care and death were around 2-fold more frequent in lung transplanted pwCF versus non-lung transplanted pwCF.

3.4 Factors associated with symptoms and worse outcomes

Univariable analyses are summarized in **Figure 4**, with full results in *Supplementary Tables 3 and 4*.

Multivariable models were fitted including only variables with <10% missing data and for response variables with sufficient events (any symptoms, pulmonary symptoms, general symptoms, hospitalisation, and oxygen therapy). No significant interactions existed between predictor variables and lung transplant in any of the multivariable models, meaning that risk factors have similar effects in non-lung transplanted and lung-transplanted pwCF. Therefore, we present multivariable analyses for all 828 pwCF with SARS-CoV-2 infection.

Factors associated with symptoms of SARS-CoV-2 infection were age >40 years, any F508del mutation, and taking pancreatic enzymes (

Figure 5). General symptoms and pulmonary symptoms were associated with any F508del mutation. Pulmonary symptoms were also associated with age ≥18 years. Additionally, use of CFTR modulators tended towards protecting against general symptoms (p=0.058) (Supplementary Table 5).

Regarding outcomes, lung transplant, CFRD, moderate and severe lung function as well as azithromycin use (often considered surrogate marker for *P. aeruginosa* infection and worse lung function) were significantly associated with hospitalisation and oxygen therapy (

Figure 5 and *Supplementary Table 6*). Age 18-29 years versus <18 years was negatively associated with oxygen therapy and CFTR modulator use was negatively associated with hospitalisation. Although multivariable models could not be fitted for the outcome death, 9/11 pwCF who died and had complete information available had at least 1 risk factor for hospitalization and/or oxygen therapy (information was incomplete for 2 adult pwCF).

4 Discussion

In this report we estimate the incidence of SARS-CoV-2 infection in pwCF in Europe to be 17.2/1000 pwCF in the year up to 31 December 2020. This is markedly higher than previous estimates of 0.7 to 4.1/1000 pwCF from earlier publications covering the first wave of the pandemic (data cut-offs before July 2020) [7, 8, 10, 11], although it is similar to an Italian estimate of 15.8/1000 pwCF up to November 2020 [12]. The data collected covers the 38-countries reporting to the ECFSPR and involves a cohort of 828 pwCF who were PCR positive for SARS-CoV-2. We also present risk factors for symptoms and worse outcomes of SARS-CoV-2 infection.

Infections between February and June 2020 (wave 1) were concentrated in Western Europe. The second wave (July to December 2020) extended towards the east and south, with higher peaks of infections. The much higher incidence in pwCF after summer 2020 reflects increased incidence in the general European population after summer 2020, which is only partly explained by different testing strategies and public restrictions [17]. Nevertheless, we probably underestimate incidence due to the voluntary nature of case reporting, burdened healthcare staff and low ECFSPR coverage (including <80% of patients) in some countries (Armenia, Belarus, Bulgaria, Lithuania, Poland, Romania, Spain, Turkey and Ukraine). Selection bias towards voluntary reporting of more severe cases cannot be excluded.

Incidence was notably higher in lung-transplanted versus non-lung transplanted pwCF (28.6 versus 16.6/1000 pwCF). Interestingly, the fold increase in incidence between the first and second waves was considerably lower for lung transplanted pwCF compared to non-transplanted pwCF (1.4-fold versus 3.8-fold, respectively). This could be due to different testing rates in the two populations, or sustained guidance that transplanted people continue highly vigilant shielding and hygiene, while non-transplanted pwCF might have resumed more activities after June [18].

Confirming our earlier report [7], around three quarters of pwCF and SARS-CoV-2 infection had symptomatic illness, lower than earlier reports from smaller CF studies (82-100%) [8, 10, 11] but similar to rates in the general population [19]. Again, this may reflect differing availability and strategy of testing different patient groups and the general population over time and between countries. The true rates of incidence as well as asymptomatic infection, can only be determined by systematic wide-scale testing of all pwCF, either in a trial or as part of routine care.

We found that pwCF mostly had general and pulmonary symptoms, as also reported in a French study [11]. Some of the most frequent symptoms of SARS-CoV-2 infection reported here are common features of CF (increased cough and pulmonary exacerbation), some less so (fever, myalgia/arthralgia). Ageusia and anosmia were uncommon symptoms in pwCF in this report (<10%) and previous CF reports [9, 11], compared to the general population (38% and 41% , respectively [20]). These surprisingly low rates may be due to high levels of missing data for these symptoms, under-reporting or concomitant sinus disease, a regular feature in CF. Of note, 71.5% of pwCF demonstrated impaired smell in a small 2012 study [21].

Factors associated with symptomatic SARS-CoV-2 infection in pwCF were age >40 years, any F508del mutation, and pancreatic insufficiency, indicating that older individuals with “classic” CF might be more prone to become symptomatic than younger pwCF with milder CFTR mutations.

Lung-transplanted pwCF had slightly higher rates of SARS-CoV-2 symptoms compared to other pwCF, confirming previous observations [8]. Transplanted individuals more often had increased dyspnoea and respiratory failure, but lower rates of increased sputum and pulmonary exacerbation, which is in line with differing lung disease phenotypes transplanted and non-transplanted pwCF.

The case fatality rate of SARS-CoV-2 infection in pwCF dropped from 3.85% up to 30 June 2020 [7] to 1.4% up to 31 December 2020, despite the higher numbers of infections during the second wave. Likewise, markedly fewer pwCF and SARS-CoV-2 infection required oxygen therapy, respiratory support, hospitalisation and intensive care in wave 2 versus wave 1. This mirrors decreased rates of intensive care and death in the general population [22] and could reflect improved management of severe cases of SARS-CoV-2 infection based on clinical experience and trials such as Recovery [23]. In CF, clinicians may have reduced precautionary hospitalisations and even intensive care admissions in favour of a more "watch and wait" approach to care, reassured by the observations that SARS-CoV-2 has a less severe impact on pwCF than initially expected. The fascinating but currently theoretical hypothesis that CFTR dysfunction may protect against SARS-CoV-2 replication in pwCF needs further investigation [24].

Solid organ transplant recipients are at increased risk of severe outcomes upon SARS-CoV-2 infection, including hospitalisation and intensive care [25-28]. In our cohort, lung transplant was associated with hospitalisation and oxygen therapy. In previous studies, lung-transplanted pwCF were more frequently treated and hospitalised [7, 8, 11]; our multivariable analysis confirms these descriptive findings in a substantial cohort of 828 pwCF. This supports recommendations that solid organ transplant recipients are vaccinated against SARS-Co-V-2. Reduced antibody response to the first mRNA vaccine dose in people after lung transplant was reported recently, however, a final conclusion on vaccination success cannot be drawn from these preliminary data and vaccination against SARS-CoV-2 continues to be strongly recommended for transplanted individuals [29].

Moderate and severe lung disease and long-term azithromycin (often considered a surrogate for worse lung disease) were also associated with hospitalisation and additional oxygen use. Moderate-severe lung disease ($ppFEV_1<70$) was also associated with hospitalisation in univariable analyses in a previous global study in pwCF [8].

Azithromycin was proposed as a possible therapy for Covid-19 but did not improve outcomes in the Recovery trial [30]. Our finding suggesting an adverse effect of long-term azithromycin use on SARS-CoV-2 outcome should be interpreted cautiously. Azithromycin has different indications in non-transplanted and transplanted pwCF, and results cannot be compared for these groups. Also, azithromycin is often considered as a surrogate for chronic *P. aeruginosa* infection and severe lung disease [31, 32], and therefore cannot be counted as independent variable in our multivariable analysis. This contributes to a strong indication bias for azithromycin, where pwCF treated with azithromycin appear to have worse outcomes. Analysing matched groups of azithromycin users and non-users could overcome this bias [33], however, this is unfeasible in our analysis. Protopathic bias could also exist for azithromycin, whereby preferential treatment of sicker patients seems to reverse cause and effect, suggesting that the treatment is associated with worsening disease. Overall, we must be cautious not to over-interpret azithromycin treatment as a risk factor for a more severe SARS-CoV-2 outcome. The identification of more advanced lung disease as a risk factor for worse outcomes supports our previous advice that pwCF need to protect their lung health by adhering to medication and physiotherapy regimens and exercise.

CFRD, reported for 26.1% pwCF in our cohort, was associated with hospitalisation and oxygen therapy, although not with symptoms. In an earlier study, hospitalisation was more frequent in pwCF with CFRD, although oxygen use was less frequent [8]. Diabetes type 1 and 2 is an established risk factor for severe outcomes with SARS-CoV-2 infection [34], but CFRD differs in mechanism and clinical impact [35]. Indeed, CFRD prevalence increases with age and could be considered as a proxy for advanced CF (creating the same potential bias as azithromycin, discussed above). Nonetheless, good control of CFRD is essential for overall health, and telehealth clinics can help pwCF and CFRD to maintain good glycaemic control during the pandemic [36].

Male sex is a risk factor for severe outcomes and death in SARS-CoV-2 [37, 38]. In our cohort, male sex was slightly underrepresented (48.4%) and not associated with symptoms or adverse outcomes. Female pwCF have a more severe clinical course of CF, culminating in younger median age at death [39]. It is possible that in our cohort the risk of worse SARS-CoV-2 outcomes in males is offset by a worse outcome for female pwCF. Further studies need to confirm this hypothesis.

Multivariable analyses in non-transplanted pwCF yielded similar risk factors. ppFEV$_1$ <70 and long-term azithromycin were associated with hospitalisation and additional oxygen use, and CFRD was associated with hospitalisation only. Altogether, these results indicate that the relevant risk factors for severe SARS-CoV-2 disease in pwCF are CFRD, lung transplantation and more advanced lung disease.

We discussed the limits of our registry-based multinational data collection in depth previously [7]. Limitations specific to the multivariable analysis include lack of context around some demographic and baseline CF characteristics. For example, the exact duration of comorbidities and concomitant medications are unknown. Some variables had high rates of missing data, due to differences in data available from national registries. Importantly, the demographic and pre-infection CF characteristics could have dated from the registry collection of the previous calendar year, depending on when SARS-CoV-2 infection occurred. Finally, SARS-CoV-2 incidence may be underestimated due to incomplete surveillance and voluntary reporting bias towards severe cases and because many mild and asymptomatic cases probably went undiagnosed. Thus, we may have overestimated severity. Similarly, surveillance for SARS-CoV-2 infection may have been more complete in certain groups than others, based on previous reports of risk factors (e.g., male sex, transplant etc. in the general and CF populations). Without a good understanding of surveillance rates, comparisons of incidence between different groups should be interpreted with caution. Prospective data collection on SARS-CoV-2 infection in pwCF in Europe is ongoing, and aims to enhance understanding, prevention and treatment of SARS-CoV-2 infection in pwCF. Future work includes long term follow-up of lung function in patients with SARS-CoV-2 versus the wider CF population, and follow-up of incidence and severity following vaccination. In future, we may need include cases diagnosed by antigen lateral flow test only, as many countries now accept a positive result as definitive, without confirmatory PCR. In addition, ECFSPR works closely together with a large global CF registry group to further improve our knowledge on SARS-CoV-2 in pwCF worldwide.

In summary, we report the first prospective study in a large cohort of pwCF infected with SARS-CoV-2 in Europe during the pandemic until the end of 2020. Clinical symptoms in pwCF are highly variable, and pulmonary symptoms resemble those from a CF exacerbation. We identified lung transplantation, CFRD and moderate to severe lung disease as independent risk factors for severe outcome after SARS-CoV-2 infection. All pwCF should maintain protective measures to prevent

SARS-CoV-2 infection and be vaccinated against SARS-CoV-2. In particular, we strongly recommend that pwCF with lung transplants, ppFEV$_1$ <70% predicted and/or CFRD shield more vigorously and be prioritised for vaccination.

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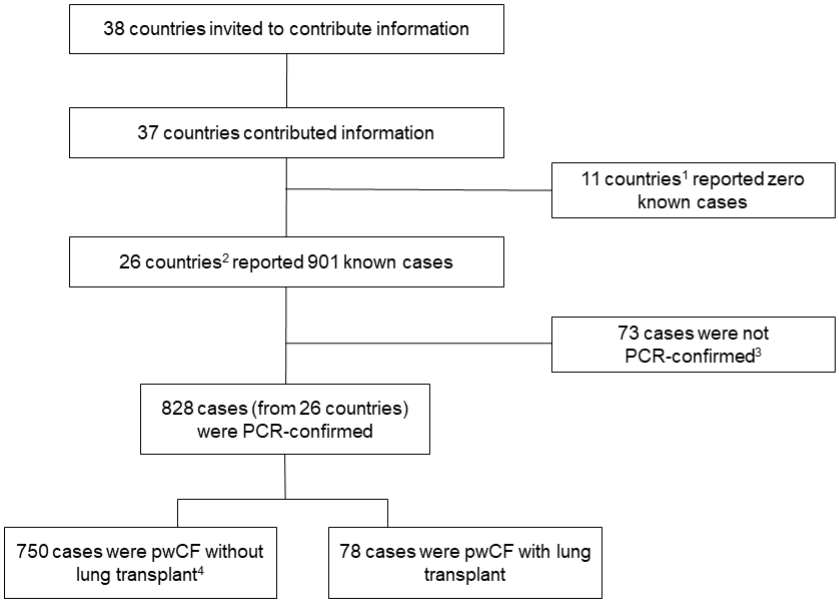

Figure 1 Data collection for people with cystic fibrosis and SARS-CoV-2 infection

1 Albania, Belarus, Bulgaria, Cyprus, Georgia, Lithuania, Luxembourg, Republic of Moldova, Romania, Serbia, Ukraine. Hungary did not report information to ECFSPR.
2 Armenia, Austria, Belgium, Croatia, Czech Republic, Denmark, France, Germany, Greece, Israel, Ireland, Italy, Latvia, Netherlands, Norway, North Macedonia, Portugal, Poland, Russia, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey, United Kingdom
3 These cases were diagnosed by antibody test, antigen test, CT scan or medical team opinion without PCR confirmation
4 This group included 10 people with non-lung solid organ transplants (7 liver, 2 kidney, 1 unspecified)

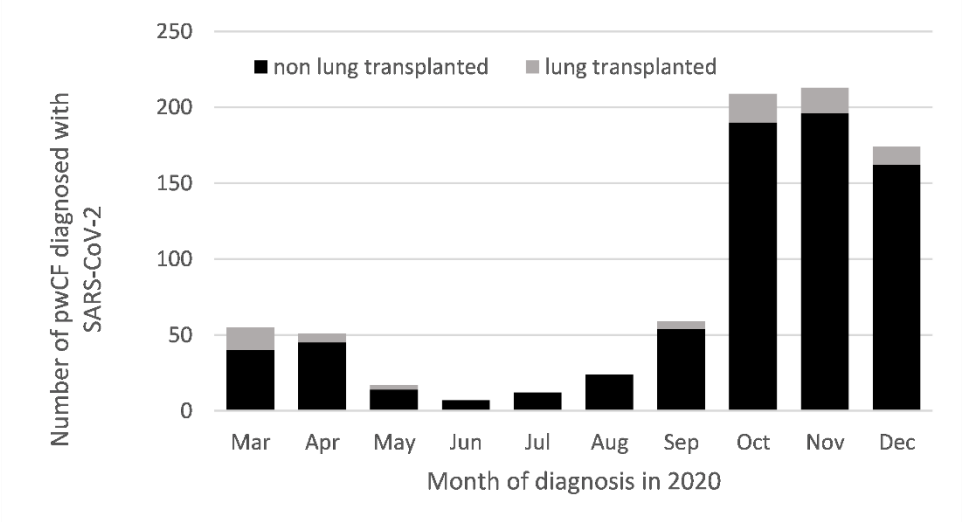

Figure 2 Diagnosis of SARS-CoV-2 infection in people with cystic fibrosis (n=828) in 2020, by month

Abbreviations: CF=cystic fibrosis, SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus 2

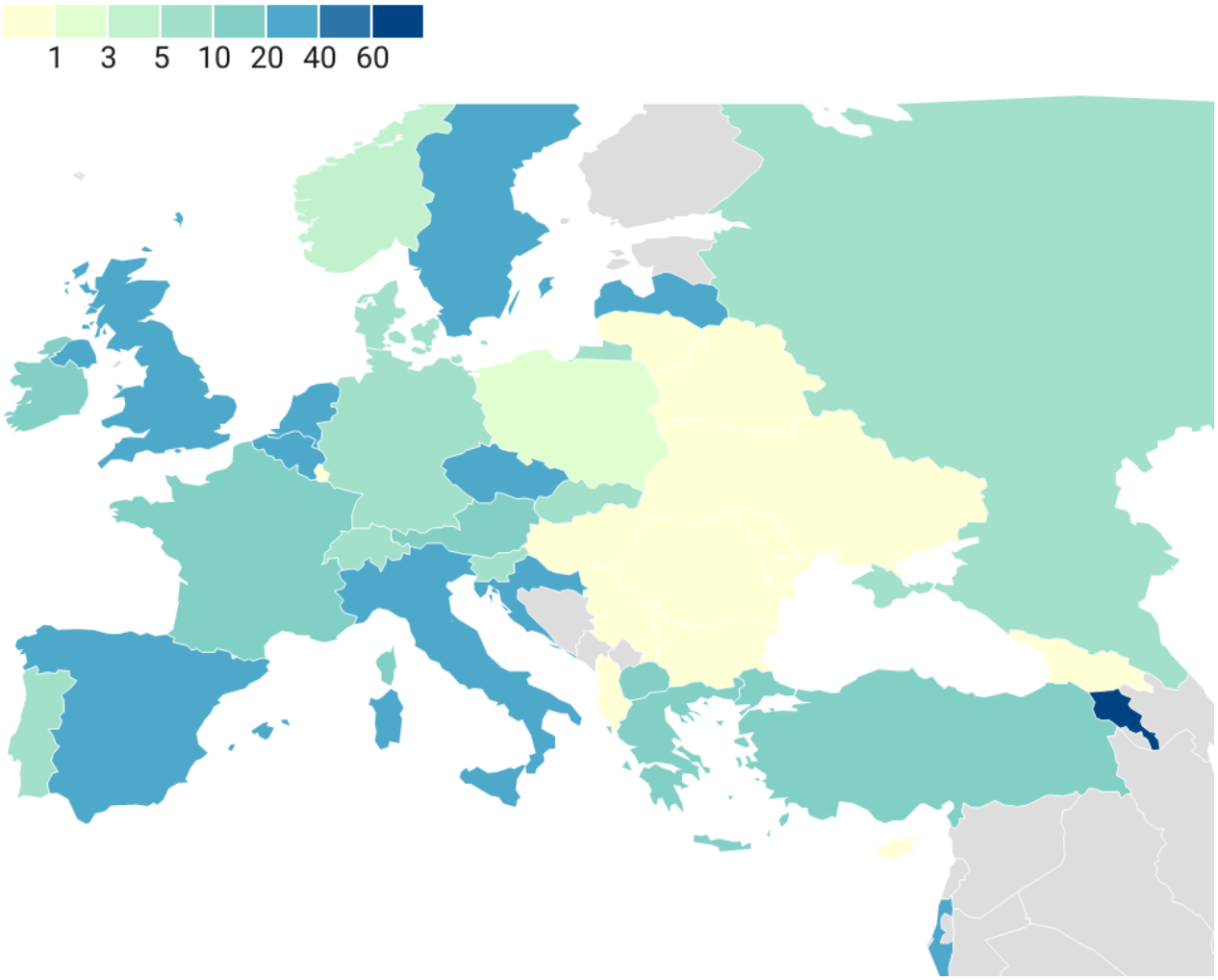

Figure 3 SARS-CoV-2 incidence per 1000 people with cystic fibrosis in 2020, by country

Abbreviations: SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus 2

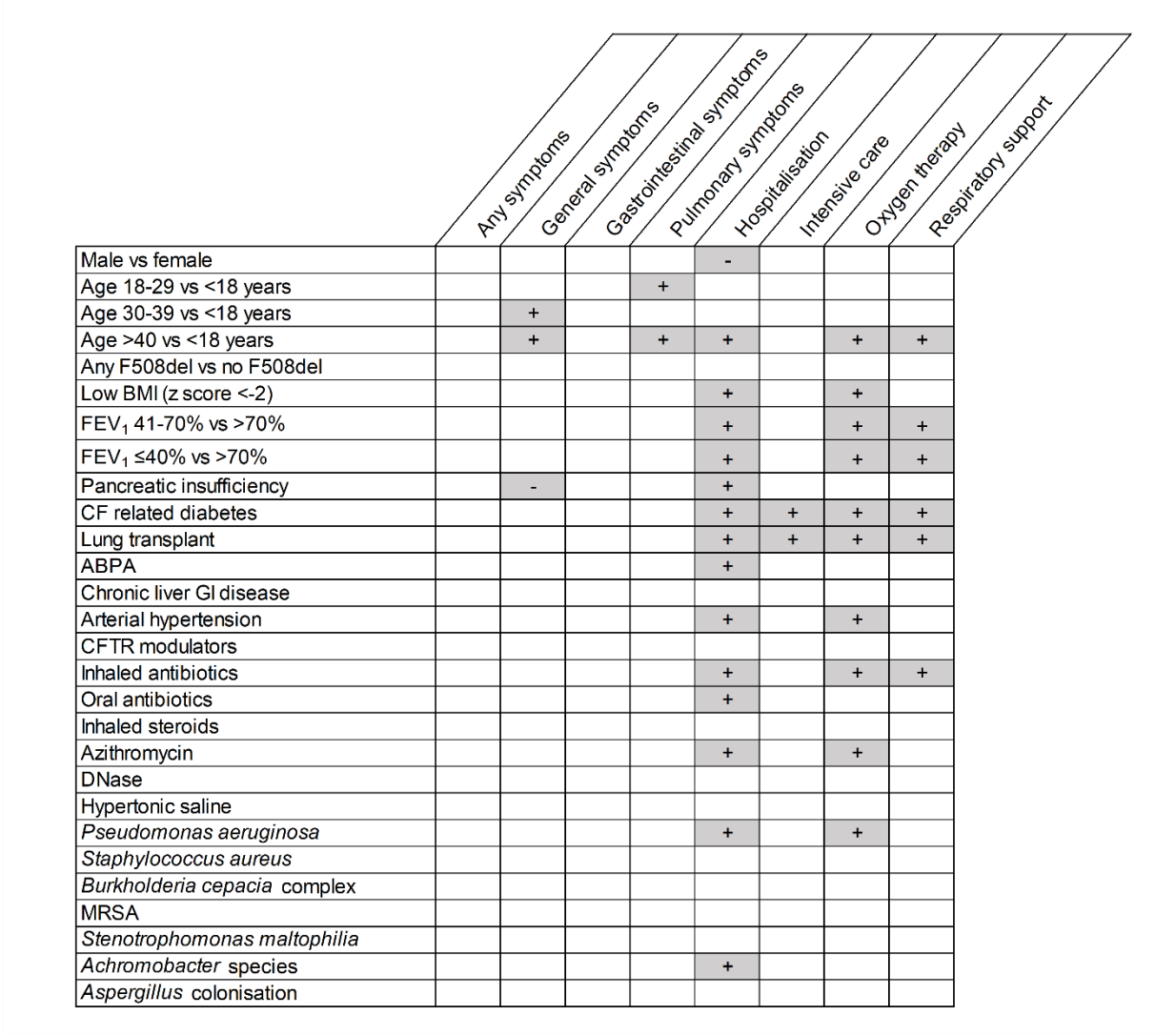

Figure 4 Factors positively (+) and negatively (-) associated with SARS-CoV-2 infection symptoms and outcomes

Abbreviations: ABPA= allergic bronchopulmonary aspergillosis, BMI=body mass index, CFTR=cystic fibrosis transmembrane conductance regulator, GI=gastrointestinal, MRSA= methicillin-resistant *Staphylococcus aureus*, ppFEV1=percent predicted forced expiratory volume.

Notes: A person was considered underweight if their BMI z score was <-2, using CDC reference values [40]

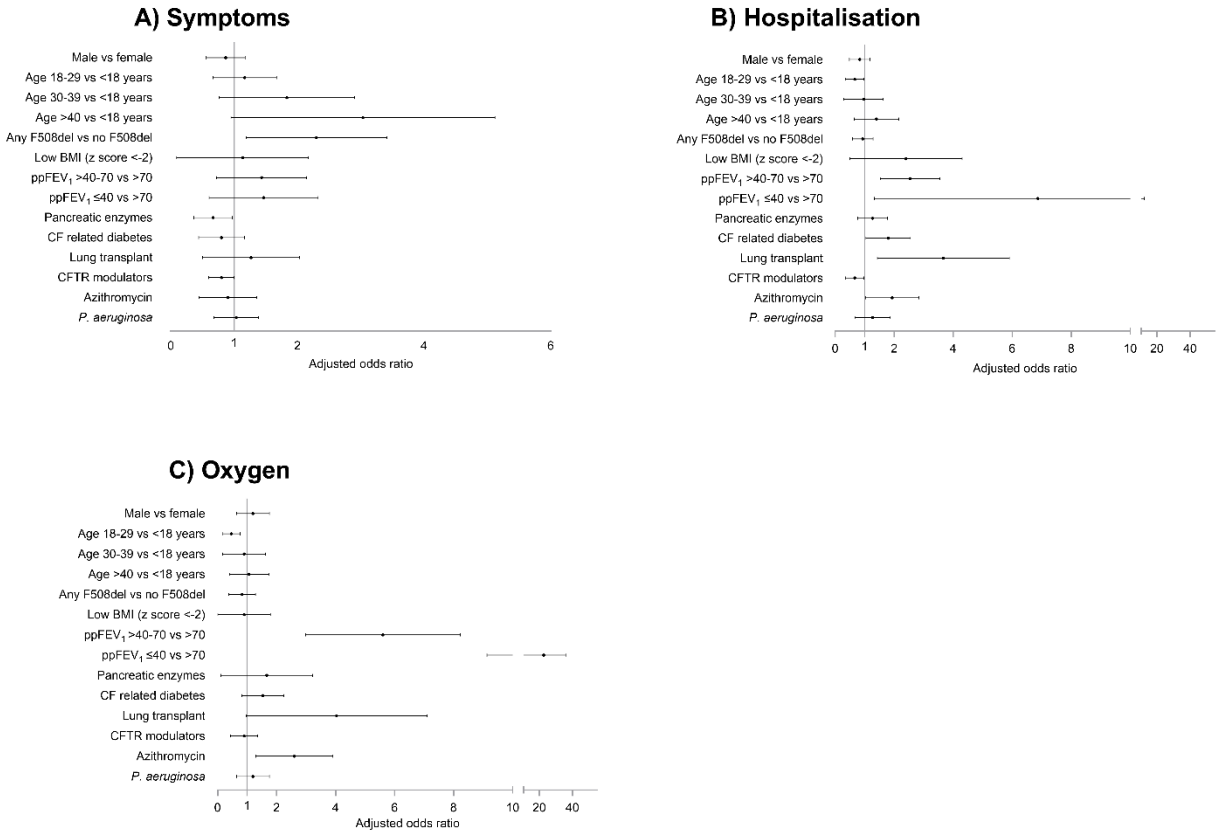

Figure 5 Multivariable analysis of factors associated with symptoms and outcomes of SARS-CoV-2 infection in people with cystic fibrosis

Abbreviations: BMI=body mass index, CFTR=cystic fibrosis transmembrane conductance regulator, $ppFEV_1$=percent predicted forced expiratory volume.

Table 1 Symptoms and outcomes of SARS-CoV-2 infection in people with CF

	Total N=828		Non-lung transplant N=750		Lung transplant N=78	
	n (%)	*Missing*	n (%)	*Missing*	n (%)	*Missing*
Symptoms						
Presence of symptoms	586 (75.7%)	*54*	528 (75.1%)	*47*	58 (81.7%)	*7*
General symptoms	467 (64.8%)	*107*	418 (64.2%)	*99*	49 (70.0%)	*8*
Fever	353 (43.9%)	*23*	311 (42.6%)	*20*	42 (56.0%)	*3*
Fatigue	228 (34.2%)	*162*	200 (33.3%)	*150*	28 (42.4%)	*12*
Myalgia or arthralgia	149 (22.4%)	*163*	128 (21.5%)	*154*	21 (30.4%)	*9*
Headache	114 (13.9%)	*10*	108 (14.6%)	*10*	6 (7.7%)	*0*
Pulmonary symptoms	405 (54.0%)	*78*	366 (53.9%)	*71*	39 (54.9%)	*7*
Increased cough	341 (43.2%)	*39*	317 (43.8%)	*26*	24 (36.9%)	*13*
Increased dyspnoea	146 (18.6%)	*43*	122 (16.9%)	*30*	24 (36.9%)	*13*
Chest tightness	45 (5.5%)	*8*	42 (5.7%)	*8*	3 (3.8%)	*0*
Wheezing	14 (1.7%)	*7*	13 (1.7%)	*7*	1 (1.3%)	*0*
Increased sputum	96 (13.9%)	*136*	93 (15.0%)	*131*	3 (4.1%)	*5*
Haemoptysis	10 (1.2%)	*4*	10 (1.3%)	*4*	0 (0.0%)	*0*
Pulmonary exacerbation	124 (21.2%)	*242*	120 (22.2%)	*210*	4 (8.7%)	*32*
Respiratory failure	15 (2.7%)	*271*	11 (2.1%)	*236*	4 (9.3%)	*35*
Gastrointestinal symptoms	70 (8.5%)	*7*	63 (8.5%)	*6*	7 (9.1%)	*1*
Diarrhoea	37 (4.5%)	*5*	33 (4.4%)	*4*	4 (5.2%)	*1*
Vomiting/nausea	26 (3.2%)	*3*	24 (3.2%)	*3*	2 (2.6%)	*0*
Abdominal pain	29 (3.5%)	*5*	26 (3.5%)	*5*	3 (3.8%)	*0*
ENT & eye symptoms	198 (34.9%)	*261*	184 (34.7%)	*220*	14 (37.8%)	*41*
Pharyngitis	95 (11.6%)	*7*	90 (12.1%)	*6*	5 (6.5%)	*1*
Conjunctivitis	8 (1.0%)	*5*	8 (1.1%)	*3*	0 (0.0%)	*2*
Acute rhinitis	83 (13.9%)	*230*	76 (13.6%)	*192*	7 (17.5%)	*38*
Acute anosmia	52 (9.0%)	*247*	49 (9.1%)	*211*	3 (7.1%)	*36*
Acute ageusia	39 (6.7%)	*249*	38 (7.1%)	*213*	1 (2.4%)	*36*
Outcomes						
Hospitalization	195 (23.7%)	*4*	156 (20.9%)	*3*	39 (50.6%)	*1*
Oxygen therapy	96 (11.7%)	*5*	76 (10.2%)	*5*	20 (25.6%)	*0*
Respiratory support	32 (3.9%)	*7*	23 (3.1%)	*7*	9 (11.5%)	*0*
Non-invasive ventilation (BIPAP, CPAP)	16 (1.9%)	*7*	13 (1.7%)	*7*	3 (3.8%)	*0*
High flow nasal canula oxygen therapy	5 (1.4%)	*475*	5 (1.5%)	*416*	0 (0.0%)	*59*
Invasive ventilation	12 (1.5%)	*8*	6 (0.8%)	*8*	6 (7.7%)	*0*
ECMO	4 (0.5%)	*71*	2 (0.3%)	*67*	2 (2.7%)	*4*
Intensive care unit	21 (2.5%)	*2*	13 (1.7%)	*2*	8 (10.3%)	*0*
Death	11 (1.4%)	*16*	7 (0.9%)	*12*	4 (5.4%)	*4*

Abbreviations: BIPAP=bilevel positive airway pressure, CPAP=continuous positive airway pressure, ECMO=extracorporeal membrane oxygenation, ENT=ear, nose and throat

Percentages were calculated on total numbers in each group (not on number of symptomatic patients/group)

Table 2 Incidence of SARS-CoV-2 infection up to 31 December 2020 in people with cystic fibrosis by lung transplant status and by age group

	All			Non-lung transplant			Lung transplant		
Age group (years)	**Cases**	**CF population**	**Incidence per 1000 (95% CI)**	**Cases**	**CF population**	**Incidence per 1000 (95% CI)**	**Cases**	**CF population**	**Incidence per 1000 (95% CI)**
Total	828	48211	17.2 (16.0 - 18.4)	750	45266	16.6 (15.4 - 17.8)	78	2729	28.6 (22.7 - 35.5)
0-11	134	17179	7.8 (6.5 - 9.2)	134	17100	7.8 (6.6 - 9.3)	0	13	0.0 (0.0 - 247.1)
12-17	113	7396	15.3 (12.6 - 18.3)	111	7278	15.3 (12.6 - 18.3)	2	84	23.8 (2.9 - 83.4)
18-29	291	12162	23.9 (21.3 - 26.8)	268	11286	23.7 (21.0 - 26.7)	23	816	28.2 (17.9 - 42)
30-39	164	6493	25.3 (21.6 - 29.4)	135	5445	24.8 (20.8 - 29.3)	29	1014	28.6 (19.2 - 40.8)
40-49	87	3280	26.5 (21.3 - 32.6)	67	2679	25.0 (19.4 - 31.7)	20	583	34.3 (21.1 - 52.5)
50+	39	1701	22.9 (16.4 - 31.2)	35	1478	23.7 (16.5 - 32.8)	4	219	18.3 (5.0 - 46.1)

Abbreviations: CF=cystic fibrosis, CI=confidence interval, SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus 2
Notes: All cases of SARS-CoV-2 in pwCF and the general population were PCR-confirmed. Incidence was calculated as (SARS-CoV-2 cases/number of people in the population)*1000. CF population size was from the 2018 ECFSPR report (2017 for France).

Table 3 Demographics and pre-infection characteristics of people with cystic fibrosis

	Total N=828		**Non-lung transplant N=750**		**Lung transplanted[1] N=78**	
	n (%)[2]	*Missing*	n (%)[2]	*Missing*	n (%)[2]	*Missing*
Gender		*0*		*0*		*0*
Female	427 (51.6%)		384 (51.2%)		43 (55.1%)	
Male	401 (48.4%)		366 (48.8%)		35 (44.9%)	
Median age (years)	24.0	*0*	23.0	*0*	34.5	*0*
0-11 years	134 (16.2%)		134 (17.9%)		0 (0%)	
12-17 years	113 (13.6%)		111 (14.8%)		2 (2.6%)	
18-29 years	291 (35.1%)		268 (35.7%)		23 (29.5%)	
30-39 years	164 (19.8%)		135 (18.0%)		29 (37.2%)	
40-49 years	87 (10.5%)		67 (8.9%)		20 (25.6%)	
>50 years	39 (4.7%)		35 (4.7%)		4 (5.1%)	
CFTR genotype		*0*		*0*		*0*
F508del/F508del	218 (26.3%)		180 (24.0%)		38 (48.7%)	
F508del/Other	262 (31.6%)		236 (31.5%)		26 (33.3%)	
Other/Other	348 (42%)		334 (44.5%)		14 (17.9%)	
BMI, z score [3]		*39*		*36*		*3*
<-2	54 (7.1%)		40 (5.8%)		14 (18.7%)	
-2 - 2	692 (90.6%)		631 (91.6%)		61 (81.3%)	
>2	18 (2.4%)		18 (2.6%)		0 (0%)	
Lung disease ($ppFEV_1$)[4]		*28*		*26*		*2*
Severe (≤40)	76 (10.3%)		65 (9.8%)		11 (14.5%)	
Moderate (>40-70)	221 (29.9%)		206 (31.0%)		15 (19.7%)	
Mild (>70)	443 (59.9%)		393 (59.2%)		50 (65.8%)	
Pancreatic insufficiency	660 (80.6%)	*9*	584 (78.8%)	*9*	76 (97.4%)	*0*
CF related diabetes	206 (26.1%)	*39*	153 (21.4%)	*34*	53 (72.6%)	*5*
ABPA	47 (7.3%)	*188*	41 (6.9%)	*158*	6 (12.5%)	*30*
Chronic liver GI disease	163 (26.6%)	*215*	148 (26.7%)	*196*	15 (25.4%)	*19*
Systemic arterial hypertension	32 (5.1%)	*199*	20 (3.4%)	*156*	12 (34.3%)	*43*
Treatment						
CFTR modulator therapy	260 (31.5%)	*2*	260 (34.8%)	*2*	0 (0.0%)	*0*
Iva	43 (5.2%)		43 (5.7%)		0 (0.0%)	
Lum/Iva	72 (8.7%)		72 (9.6%)		0 (0.0%)	
Tez/Iva	75 (9.1%)		75 (10.0%)		0 (0.0%)	
Elexa/Tez/Iva	63 (7.6%)		63 (8.4%)		0 (0.0%)	
Yes, type unknown	4 (0.5%)		4 (0.5%)		0 (0.0%)	
Yes, other	3 (0.4%)		3 (0.4%)		0 (0.0%)	
Inhaled antibiotics	332 (50.7%)	*173*	313 (50.6%)	*131*	19 (52.8%)	*42*
Oral antibiotics	234 (38.5%)	*220*	215 (37.3%)	*174*	19 (59.4%)	*46*
Inhaled steroid	318 (42.0%)	*71*	302 (43.7%)	*59*	16 (24.2%)	*12*
Azithromycin	307 (38.1%)	*22*	253 (34.7%)	*21*	54 (70.1%)	*1*
DNase	382 (58.3%)	*173*	377 (60.9%)	*131*	5 (13.9%)	*42*
Hypertonic Saline	338 (51.4%)	*171*	334 (53.8%)	*129*	4 (11.1%)	*42*
Flu vaccine	207 (57.8%)	*470*	180 (55.6%)	*426*	27 (79.4%)	*44*
Microbiology						
Pseudomonas aeruginosa	346 (43.4%)	*31*	313 (42.6%)	*15*	33 (53.2%)	*16*
Staphylococcus aureus	420 (57.7%)	*100*	403 (59.0%)	*67*	17 (37.8%)	*33*
Burkholderia cepacia complex	29 (4.4%)	*168*	28 (4.5%)	*122*	1 (3.1%)	*46*
MRSA	65 (9.3%)	*126*	63 (9.5%)	*84*	2 (5.6%)	*42*
Non-tuberculous mycobacteria	28 (5.2%)	*292*	28 (5.5%)	*242*	0 (0.0%)	*50*
Stenotrophomonas maltophilia	65 (8.8%)	*90*	63 (9.1%)	*61*	2 (4.1%)	*29*

Achromobacter species	60 (8.1%)	*89*	54 (7.8%)	*61*	6 (12.0%)	*28*
Aspergillus colonisation	102 (14.0%)	*99*	94 (13.8%)	*71*	8 (16.0%)	*28*

Abbreviations: ABPA= allergic bronchopulmonary aspergillosis, BMI=body mass index, CFTR=cystic fibrosis transmembrane conductance regulator, Elexa=elexacaftor, GI=gastrointestinal, Iva=ivacaftor, Lum=lumacaftor, MRSA= methicillin-resistant *Staphylococcus aureus*, ppFEV1=percent predicted forced expiratory volume, Tez=tezacaftor

Notes:

1 Ten recipients of other solid organ transplants were included in this group (7 liver, 2 kidney, 1 unspecified)
2 Percentages are computed excluding missing data.
3 BMI z-score was only calculated for patients aged 2 years and over, using CDC reference values [40]
4 $ppFEV_1$ was only calculated for patients aged 6 years and over

References

1. World Health Organisation. Weekly epidemiological update - 29 December 2020. https://www.who.int/publications/m/item/weekly-epidemiological-update---29-december-2020 Date last updated: 29 December 2020, Date last accessed: 23 March 2021

2. Viviani L, Assael BM, Kerem E, et al. Impact of the A (H1N1) pandemic influenza (season 2009-2010) on patients with cystic fibrosis. *J Cyst Fibros* 2011: 10(5): 370-376.

3. Kiedrowski MR, Bomberger JM. Viral-Bacterial Co-infections in the Cystic Fibrosis Respiratory Tract. *Front Immunol* 2018: 9: 3067.

4. Dennis JB, Jones AM, Davies EA, et al. Influenza B outbreak at an adult cystic fibrosis centre - Clinical impact and factors influencing spread. *J Cyst Fibros* 2020: 19(5): 808-814.

5. Colombo C, Burgel PR, Gartner S, et al. Impact of COVID-19 on people with cystic fibrosis. *The Lancet Respiratory medicine* 2020: 8(5): e35-e36.

6. van Koningsbruggen-Rietschel S, Dunlevy F, Bulteel V, et al. SARS-CoV-2 disrupts clinical research: the role of a rare disease-specific trial network. *Eur Respir J* 2020: 56(3): 2002114.

7. Naerlich et al. Incidence of SARS-CoV-2 in people with cystic fibrosis in Europe between February and June 2020. *J Cyst Fibros* 2021: Apr 18;S1569-1993(21)00099-0. doi: 10.1016/j.jcf.2021.03.017. Online ahead of print.

8. McClenaghan E, Cosgriff R, Brownlee K, et al. The global impact of SARS-CoV-2 in 181 people with cystic fibrosis. *J Cyst Fibros* 2020: 19(6): 868-871.

9. Bain R, Cosgriff R, Zampoli M, et al. Clinical characteristics of SARS-CoV-2 infection in children with cystic fibrosis: An international observational study. *J Cyst Fibros* 2021: 20(1): 25-30.

10. Mondejar-Lopez P, Quintana-Gallego E, Giron-Moreno RM, et al. Impact of SARS-CoV-2 infection in patients with cystic fibrosis in Spain: Incidence and results of the national CF-COVID19-Spain survey. *Respir Med* 2020: 170(1532-3064 (Electronic)): 106062.

11. Corvol H, de Miranda S, Lemonnier L, et al. First Wave of COVID-19 in French Patients with Cystic Fibrosis. *J Clin Med* 2020: 9(11): 3624.

12. Padoan R, Carnovale V, Salvatore D, et al. First and second wave of SARS-CoV2 in Italian Cystic Fibrosis patients: Data from Italian Cystic Fibrosis Registry. *J Cyst Fibros* 2021: 26: S1569-1993.

13. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J* 2005: 26(5): 948-968.

14. Zolin A, Orenti A, Naehrlich L, et al. ECFS Patient Registry Annual Report 2018. https://www.ecfs.eu/projects/ecfs-patient-registry/annual-reports Date last updated: 2020, Date last accessed:

15. Zolin A, Orenti A, Naehrlich L, et al. ECFS Patient Registry Annual Report 2017. https://www.ecfs.eu/projects/ecfs-patient-registry/annual-reports Date last updated: 2019, Date last accessed:

16. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. *Am J Epidemiol* 2007: 165(6): 710-718.

17. European Centre for Disease Control. Data on testing for COVID-19 by week and country. 2020.

18. International Society of Heart and Lung Transplantation (ISHLT). Guidance from the International Society of Heart and Lung Transplantation regarding the SARS CoV-2 pandemic https://ishlt.org/ishlt/media/documents/SARS-CoV-2_Guidance-for-Cardiothoracic-Transplant-and-VAD-center.pdf Date last updated: 1 February 2021, Date last accessed: 31 March 2021

19. Buitrago-Garcia D, Egli-Gany D, Counotte MJ, et al. Occurrence and transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections: A living systematic review and meta-analysis. *PLoS Med* 2020: 17(9): e1003346.

20. Agyeman AA, Chin KL, Landersdorfer CB, et al. Smell and Taste Dysfunction in Patients With COVID-19: A Systematic Review and Meta-analysis. *Mayo Clin Proc* 2020: 95(8): 1621-1631.

21. Lindig J, Steger C, Beiersdorf N, et al. Smell in cystic fibrosis. *Eur Arch Otorhinolaryngol* 2013: 270(3): 915-921.

22. Karagiannidis C, Windisch W, McAuley DF, et al. Major differences in ICU admissions during the first and second COVID-19 wave in Germany. *The Lancet Respiratory medicine* 2021.

23. Chalmers JD, Crichton ML, Goeminne PC, et al. Management of hospitalised adults with coronavirus disease-19 (COVID-19): A European Respiratory Society living guideline. *Eur Respir J* 2021.

24. Peckham D, McDermott MF, Savic S, et al. COVID-19 meets Cystic Fibrosis: for better or worse? *Genes Immun* 2020: 21(4): 260-262.

25. Centers for disease control and prevention (CDC). Evidence used to update the list of underlying medical conditions that increase a person's risk of severe illness from COVID-19. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/evidence-table.html Date last updated: 29 March 2021, Date last accessed: 22 December 2020

26. Raja MA, Mendoza MA, Villavicencio A, et al. COVID-19 in solid organ transplant recipients: A systematic review and meta-analysis of current literature. *Transplant Rev (Orlando)* 2021: 35(1): 100588.

27. Saez-Gimenez B, Berastegui C, Barrecheguren M, et al. COVID-19 in lung transplant recipients: A multicenter study. *Am J Transplant* 2020.

28. Kapriniotis K, Giannis D, Geropoulos G, et al. Heart and Lung Transplantation in the Era of COVID-19: Early Recommendations and Outcomes. *Exp Clin Transplant* 2021.

29. International Society of Heart and Lung Transplantation (ISHLT). SARS-CoV-2 Vaccination in Heart and Lung Transplantation, Recommendations from the ISHLT COVID-19 Task Force. https://ishlt.org/ishlt/media/Documents/COVID19_Vaccine-Recommendations_3-15-2021.pdf Date last updated: 15 March 2021, Date last accessed: 31 March 2021

30. RECOVERY Collaborative Group. Azithromycin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021: 397(10274): 605-612.

31. Saiman L, Siegel J. Infection control in cystic fibrosis. *Clin Microbiol Rev* 2004: 17(1): 57-71.

32. Castellani C, Duff AJA, Bell SC, et al. ECFS best practice guidelines: the 2018 revision. *J Cyst Fibros* 2018: 17(2): 153-178.

33. Nichols DP, Odem-Davis K, Cogen JD, et al. Pulmonary Outcomes Associated with Long-Term Azithromycin Therapy in Cystic Fibrosis. *Am J Respir Crit Care Med* 2020: 201(4): 430-437.

34. McGurnaghan SJ, Weir A, Bishop J, et al. Risks of and risk factors for COVID-19 disease in people with diabetes: a cohort study of the total population of Scotland. *The lancet Diabetes & endocrinology* 2021: 9(2): 82-93.

35. Bridges N, Rowe R, Holt RIG. Unique challenges of cystic fibrosis-related diabetes. *Diabet Med* 2018.

36. Hasan S, Cecilia Lansang M, Salman Khan M, et al. Managing Cystic Fibrosis related diabetes via telehealth during COVID-19 pandemic. *Journal of clinical & translational endocrinology* 2021: 23: 100253.

37. Booth A, Reed AB, Ponzo S, et al. Population risk factors for severe disease and mortality in COVID-19: A global systematic review and meta-analysis. *PLoS One* 2021: 16(3): e0247461.

38. Peckham H, de Gruijter NM, Raine C, et al. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. *Nature communications* 2020: 11(1): 6317.

39. Lam GY, Goodwin J, Wilcox PG, et al. Sex disparities in cystic fibrosis: review on the effect of female sex hormones on lung pathophysiology and outcomes. *ERJ Open Research* 2021: 7(1): 00475-02020.

40. Kuczmarski RJ, Ogden CL, Guo SS, et al. 2000 CDC Growth Charts for the United States: methods and development. *Vital Health Stat 11* 2002(246): 1-190.

Factors for severe outcomes following SARS-CoV-2 infection in people with cystic fibrosis

Supplementary Information

Supplementary Table 1 Number and incidence of SARS-CoV-2 infections in people with cystic fibrosis, by wave and by country.

	Feb-Dec 2020			Wave 1 (Feb-June)			Wave 2 (Jul-Dec)		
Country	**Cases**	**CF population**	**Incidence per 1000 (95% CI)**	**Cases**	**CF population**	**Incidence per 1000 (95% CI)**	**Cases**	**CF population**	**Incidence per 1000 (95% CI)**
Armenia	2	28	71.4 (8.8 – 235.0)	0	28	0.0 (0.0 - 123.4)	2	28	71.4 (8.8 – 235.0)
Austria	13	793	16.4 (8.8 - 27.9)	0	793	0.0 (0.0 - 4.6)	13	793	16.4 (8.8 - 27.9)
Belgium	43	1298	33.1 (24.1 - 44.4)	6	1298	4.6 (1.7 - 10)	37	1298	28.5 (20.1 - 39.1)
Croatia	4	123	32.5 (8.9 - 81.2)	0	123	0.0 (0.0 - 29.5)	4	123	32.5 (8.9 - 81.2)
Czech Republic	24	615	39.0 (25.2 - 57.5)	0	615	0.0 (0.0 - 6)	24	615	39.0 (25.2 - 57.5)
Denmark	5	512	9.8 (3.2 - 22.6)	2	512	3.9 (0.5 - 14)	3	512	5.9 (1.2 – 17.0)
France	104	6940	15.0 (12.3 - 18.1)	19	6940	2.7 (1.6 - 4.3)	85	6940	12.2 (9.8 - 15.1)
Germany	44	6361	6.9 (5.0 - 9.3)	17	6361	2.7 (1.6 - 4.3)	27	6361	4.2 (2.8 - 6.2)
Greece	6	588	10.2 (3.8 - 22.1)	2	588	3.4 (0.4 - 12.2)	4	588	6.8 (1.9 - 17.3)
Ireland	14	1224	11.4 (6.3 - 19.1)	5	1224	4.1 (1.3 - 9.5)	9	1224	7.4 (3.4 - 13.9)
Israel	19	537	35.4 (21.4 - 54.7)	0	537	0.0 (0.0 - 6.8)	19	537	35.4 (21.4 - 54.7)
Italy	159	5501	28.9 (24.6 - 33.7)	17	5501	3.1 (1.8 - 4.9)	142	5501	25.8 (21.8 - 30.4)
Latvia	1	37	27.0 (0.7 - 141.6)	0	37	0.0 (0.0 - 94.9)	1	37	27.0 (0.7 - 141.6)
Netherlands	40	1394	28.7 (20.6 - 38.9)	4	1394	2.9 (0.8 - 7.3)	36	1394	25.8 (18.2 - 35.6)
North Macedonia	2	119	16.8 (2.0 - 59.4)	0	119	0.0 (0.0 - 30.5)	2	119	16.8 (2.0 - 59.4)
Norway	1	290	3.4 (0.1 - 19.1)	1	290	3.4 (0.1 - 19.1)	0	290	0.0 (0.0 - 12.6)
Poland	2	882	2.3 (0.3 - 8.2)	2	882	2.3 (0.3 - 8.2)	0	882	0.0 (0.0 - 4.2)
Portugal	2	296	6.8 (0.8 - 24.2)	0	296	0.0 (0.0 - 12.4)	2	296	6.8 (0.8 - 24.2)
Russia	30	3137	9.6 (6.5 - 13.6)	6	3137	1.9 (0.7 - 4.2)	24	3137	7.7 (4.9 - 11.4)
Slovak Republic	2	278	7.2 (0.9 - 25.7)	0	278	0.0 (0.0 - 13.2)	2	278	7.2 (0.9 - 25.7)
Slovenia	1	109	9.2 (0.2 - 50.1)	0	109	0.0 (0.0 - 33.3)	1	109	9.2 (0.2 - 50.1)
Spain	58	2192	26.5 (20.2 - 34.1)	11	2192	5.0 (2.5 – 9.0)	47	2192	21.4 (15.8 - 28.4)

	Feb-Dec 2020			Wave 1 (Feb-June)			Wave 2 (Jul-Dec)		
Country	**Cases**	**CF population**	**Incidence per 1000 (95% CI)**	**Cases**	**CF population**	**Incidence per 1000 (95% CI)**	**Cases**	**CF population**	**Incidence per 1000 (95% CI)**
Sweden	19	689	27.6 (16.7 - 42.7)	6	689	8.7 (3.2 - 18.9)	13	689	18.9 (10.1 – 32.0)
Switzerland	9	950	9.5 (4.3 - 17.9)	3	950	3.2 (0.7 - 9.2)	6	950	6.3 (2.3 - 13.7)
Turkey	26	1807	14.4 (9.4 - 21)	3	1807	1.7 (0.3 - 4.8)	23	1807	12.7 (8.1 – 19.0)
United Kingdom	198	9847	20.1 (17.4 - 23.1)	26	9847	2.6 (1.7 - 3.9)	172	9847	17.5 (15.0 - 20.3)
Sum	828	48211	17.2 (16 - 18.4)	130	48211	2.7 (2.3 - 3.2)	698	48211	14.5 (13.4 - 15.6)

Abbreviations: CF=cystic fibrosis, CI=confidence interval, SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus 2

The following countries reported zero cases of SARS-CoV-2 in people with CF till 31 December 2020: Albania, Belarus, Bulgaria, Cyprus, Georgia, Lithuania, Luxembourg, Republic of Moldova, Romania, Serbia, Ukraine. One country (Hungary) did not report information to ECFSPR.

Supplementary Table 2 Characteristics of people with cystic fibrosis and SARS-CoV-2 infection who died

			Number of patients (n=11)
Demographics	Gender	Female	5
		Male	6
	Age	0-11 years	3
		12-17 years	1
		18-29 years	2
		30-39 years	2
		40-49 years	3
	BMI, z score [1]	Missing	1
		<-2	3
		-2 - 2	7
Cystic fibrosis pre-infection characteristics	Lung transplant[2]		4
	CFTR genotype	Other/other	3
		F508del/other	2
		F508del/F508del	6
	Lung disease ($ppFEV_1$)[3]	Missing	2
		Severe (≤40%)	4
		Moderate (>40-70%)	4
		Mild (>70%)	1
	Pseudomonas aeruginosa		6
	CF related diabetes		7
	Pancreatic insufficiency		11
Outcomes	Oxygen therapy		9
	Respiratory support		7
	Hospital		10
	Intensive care		6
Cause of death	SARS-CoV-2 infection		8
	Other[4]		1
	Unknown[5]		2

Abbreviations: BMI=body mass index, CFTR=cystic fibrosis transmembrane conductance regulator, ppFEV1=percent predicted forced expiratory volume

1 BMI z-score was only calculated for patients aged 2 years and over

2 No patient who died had received transplant of a solid organ other than lung

3 $ppFEV_1$ was only calculated for patients aged 6 years and over

4 This was a paediatric lung-transplanted patient.

5 Both were adults who died within 3 months of SARS-CoV-2 infection

Supplementary Table 3 Univariable analysis of the association of demographics and cystic fibrosis characteristics with symptoms of SARS-CoV-2 infection in people with cystic fibrosis

Characteristics of pwCF		**Presence of symptoms**		**General symptoms**		**Gastrointestinal symptoms**		**Pulmonary symptoms**	
		Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Gender	male vs female	0.9 (0.6 - 1.2)	0.712	1.1 (0.7 - 1.5)	0.914	1.1 (0.7 - 1.6)	0.898	0.8 (0.6 - 1.0)	0.208
Age	18-29 vs 0-17 years	1.3 (0.9 - 1.8)	0.430	1.7 (1.1 - 2.5)	0.098	0.7 (0.4 - 1.2)	0.674	1.8 (1.3 - 2.6)	0.014
	30-39 vs 0-17 years	1.9 (1.2 - 3.1)	0.112	2.4 (1.5 - 3.8)	<0.001	0.8 (0.4 - 1.5)	0.683	2.1 (1.1 - 4.3)	0.140
	40+ vs 0-17 years	3.8 (1.7 - 8.9)	0.056	4.7 (2.5 - 9.0)	<0.001	0.5 (0.1 - 1.7)	0.674	4.9 (2.8 - 8.8)	<0.001
Genotype	Any F508del vs no F508del	1.9 (1.1 - 3.1)	0.117	1.7 (0.9 - 3.1)	0.378	1.3 (0.3 - 5.3)	0.897	1.2 (0.9 - 1.6)	0.405
BMI underweight[1]	Yes vs No	0.8 (0.4 - 1.7)	0.823	0.9 (0.5 - 1.7)	0.914	1.9 (0.9 - 3.9)	0.674	0.9 (0.5 - 1.6)	0.857
Lung function (FEV1 % predicted)	>40-70% vs >70%	1.2 (0.7 - 2.1)	0.712	1.3 (0.8 - 2.1)	0.600	1.2 (0.7 - 1.9)	0.775	1.5 (1.1 - 2.2)	0.121
	≤40% vs >70%	1.2 (0.7 – 2.0)	0.823	1.3 (0.8 - 2.2)	0.635	1.2 (0.7 - 2.2)	0.778	1.8 (1.1 - 3.1)	0.118
Pancreatic insufficiency	Yes vs No	0.7 (0.5 - 0.9)	0.117	0.6 (0.4 - 0.8)	0.028	0.7 (0.4 - 1.4)	0.674	0.7 (0.5 - 0.9)	0.070
CF related diabetes	Yes vs No	0.8 (0.5 - 1.4)	0.809	1.0 (0.6 - 1.5)	0.914	0.7 (0.3 - 1.4)	0.674	1.1 (0.8 - 1.7)	0.779
Lung transplant	Yes vs No	1.5 (0.9 - 2.4)	0.389	1.3 (0.9 - 1.9)	0.600	1.1 (0.4 - 3.3)	0.936	1.0 (0.7 - 1.5)	0.890
ABPA	Yes vs No	1.2 (0.4 - 3.1)	0.933	1.0 (0.5 - 2.1)	0.994	0.6 (0.1 - 2.4)	0.683	1.8 (1.0 - 3.4)	0.148
Chronic liver GI disease	Yes vs No	1.1 (0.6 – 2.0)	0.897	1.2 (0.8 - 1.8)	0.754	0.7 (0.3 - 1.5)	0.674	1.0 (0.7 - 1.3)	0.857
Systemic arterial hypertension	Yes vs No	1.9 (1.0 - 3.8)	0.216	1.7 (0.9 - 3.2)	0.356	3.0 (1.4 - 6.4)	0.168	2.1 (1.0 - 4.2)	0.147
CFTR modulator therapy	Yes vs No	0.8 (0.6 - 1.1)	0.406	0.8 (0.6 - 1.1)	0.600	0.6 (0.2 - 1.7)	0.676	1.0 (0.7 - 1.4)	0.898

Characteristics of pwCF		**Presence of symptoms**		**General symptoms**		**Gastrointestinal symptoms**		**Pulmonary symptoms**	
Inhaled antibiotics	Yes vs No	0.7 (0.5 - 1.2)	0.430	1.0 (0.6 - 1.6)	0.948	0.7 (0.4 - 1.2)	0.674	1.1 (0.7 - 1.8)	0.779
Oral antibiotics	Yes vs No	0.6 (0.4 - 0.9)	0.117	0.7 (0.4 - 1.2)	0.600	0.4 (0.1 - 1.4)	0.674	1.3 (0.9 - 1.7)	0.325
Inhaled steroid	Yes vs No	1.1 (0.8 - 1.7)	0.823	1.2 (0.8 - 1.6)	0.675	1.0 (0.5 - 2.2)	0.936	1.3 (1.0 - 1.8)	0.208
Azithromycin	Yes vs No	1.0 (0.6 - 1.5)	0.933	1.1 (0.7 - 1.7)	0.914	0.9 (0.5 - 1.6)	0.897	1.5 (1.0 - 2.3)	0.148
DNase	Yes vs No	0.8 (0.5 - 1.1)	0.347	0.8 (0.6 - 1.0)	0.134	0.6 (0.3 - 1.2)	0.674	0.8 (0.6 - 1.2)	0.369
Hypertonic Saline	Yes vs No	0.8 (0.6 - 1.1)	0.417	0.8 (0.6 - 1.1)	0.600	1.1 (0.6 - 2.0)	0.898	1 (0.7 - 1.4)	1.000
Pseudomonas aeruginosa	Yes vs No	1.4 (1.1 - 1.8)	0.117	1.4 (1.0 - 1.9)	0.238	0.5 (0.3 - 1.0)	0.462	1.6 (1.1 - 2.3)	0.056
Staphylococcus aureus	Yes vs No	1.0 (0.6 - 1.6)	0.997	0.9 (0.6 - 1.5)	0.914	1.1 (0.5 - 2.4)	0.898	0.9 (0.7 - 1.1)	0.369
Burkholderia cepacia complex	Yes vs No	1.0 (0.6 - 1.7)	0.980	1.1 (0.5 - 2.3)	0.914	1 (0.3 - 3.9)	0.943	1.2 (0.6 - 2.3)	0.779
MRSA	Yes vs No	0.9 (0.5 - 1.7)	0.933	1.1 (0.6 - 2.2)	0.914	1.7 (0.6 - 4.7)	0.674	0.7 (0.4 - 1.1)	0.321
Stenotrophomonas maltophilia	Yes vs No	0.9 (0.5 - 1.6)	0.933	0.8 (0.5 - 1.3)	0.675	0.7 (0.3 - 1.8)	0.683	1.4 (0.8 - 2.2)	0.369
Achromobacter species	Yes vs No	0.9 (0.5 - 1.9)	0.933	1.0 (0.6 - 1.7)	0.948	1.7 (0.7 - 3.8)	0.674	1.3 (0.6 - 2.6)	0.704
Aspergillus colonisation	Yes vs No	1.3 (0.9 - 1.9)	0.430	1.2 (0.8 - 1.9)	0.600	1.5 (0.6 - 3.6)	0.674	1.2 (0.9 - 1.7)	0.325

Abbreviations: ABPA= allergic bronchopulmonary aspergillosis, BMI=body mass index, CFTR=cystic fibrosis transmembrane conductance regulator, GI=gastrointestinal, MRSA= methicillin-resistant *Staphylococcus aureus*, FEV1=percent predicted forced expiratory volume, Iva=ivacaftor, Tez=tezacaftor, Lum=lumacaftor, Elexa=elexacaftor

p-values are adjusted for multiple comparison using False Discovery Rate method.

1 A person was considered underweight if their BMI z score was <-2

Supplementary Table 4 Univariable analysis of the association of demographics and cystic fibrosis characteristics with outcomes of SARS-CoV-2 infection in people with cystic fibrosis

Characteristics of pwCF		**Hospitalization**		**ICU**		**Oxygen therapy**		**Respiratory support**	
		Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Gender	male vs female	0.7 (0.5 - 0.9)	0.037	1.2 (0.6 - 2.3)	0.716	0.9 (0.5 - 1.3)	0.610	1.1 (0.5 - 2.2)	0.982
Age	18-29 vs 0-17 years	1.0 (0.8 - 1.4)	0.883	0.7 (0.2 – 2.0)	0.676	1.0 (0.6 - 1.7)	0.892	0.5 (0.2 - 1.6)	0.518
	30-39 vs 0-17 years	1.5 (0.9 - 2.5)	0.191	1.5 (0.4 - 5.8)	0.685	1.6 (0.6 - 4.3)	0.427	1.5 (0.6 - 3.8)	0.616
	40+ vs 0-17 years	2.4 (1.6 - 3.6)	<0.001	2.9 (0.9 - 9.1)	0.202	2.4 (1.4 - 4.2)	0.008	2.9 (1.3 - 6.2)	0.032
Genotype	Any F508del vs no F508del	1.0 (0.7 - 1.3)	0.905	1.8 (1.1 - 3.2)	0.144	0.8 (0.5 - 1.4)	0.541	1.2 (0.6 - 2.3)	0.708
BMI underweight[1]	Yes vs No	3.8 (2.1 – 7.0)	<0.001	1.5 (0.5 - 4.8)	0.685	3.1 (1.7 - 5.7)	<0.001	2.0 (0.7 - 5.6)	0.405
Lung function (FEV1 % predicted)	>40-70% vs >70%	2.7 (2.0 - 3.6)	<0.001	2.3 (1.1 - 5.1)	0.144	5.4 (3.0 - 9.5)	<0.001	5.7 (2.3 – 14.0)	<0.001
	≤40% vs >70%	8.1 (4.0 - 16.5)	<0.001	2.6 (0.7 - 9.7)	0.387	18.2 (9.4 - 35.2)	<0.001	8.5 (2.9 - 25.2)	<0.001
Pancreatic insufficiency	Yes vs No	1.8 (1.2 - 2.5)	0.005	2.3 (0.5 - 10.8)	0.487	1.8 (0.9 - 3.7)	0.224	1.7 (0.6 - 4.6)	0.525
CF related diabetes	Yes vs No	2.6 (1.9 - 3.7)	<0.001	4.6 (2.3 - 9.5)	<0.001	2.1 (1.6 - 2.9)	<0.001	3.2 (1.7 - 5.8)	<0.001
Lung transplant	Yes vs No	3.9 (2.8 - 5.4)	<0.001	6.5 (3.2 - 13.2)	<0.001	3.0 (2.1 - 4.5)	<0.001	4.1 (2.2 - 7.5)	<0.001
ABPA	Yes vs No	2.5 (1.5 - 4.2)	<0.001	1.8 (0.6 - 6.1)	0.499	1.9 (1.1 - 3.3)	0.066	1.1 (0.2 - 5.2)	0.988
Chronic liver GI disease	Yes vs No	1.1 (0.9 - 1.5)	0.459	1.3 (0.5 - 3.5)	0.716	1.5 (1.0 - 2.2)	0.164	1.0 (0.5 - 2.1)	0.988
Systemic arterial hypertension	Yes vs No	3.1 (1.8 - 5.4)	<0.001	5.5 (1.1 – 27.0)	0.144	3.2 (1.7 - 5.9)	<0.001	3.1 (1.1 - 9.2)	0.109

Characteristics of pwCF		**Hospitalization**		**ICU**		**Oxygen therapy**		**Respiratory support**	
CFTR modulator therapy	Yes vs No	0.7 (0.5 – 1.0)	0.058	0.5 (0.2 - 1.2)	0.313	0.9 (0.6 - 1.3)	0.620	0.6 (0.3 - 1.1)	0.287
Inhaled antibiotics	Yes vs No	1.9 (1.1 - 3.5)	0.049	5.5 (1.2 – 25.0)	0.144	3.1 (1.9 – 5.0)	<0.001	6.8 (1.9 – 25.0)	0.019
Oral antibiotics	Yes vs No	1.5 (1.1 - 2.1)	0.038	3.7 (1.3 - 10.5)	0.140	1.6 (1.0 - 2.7)	0.154	2.0 (0.8 - 4.7)	0.287
Inhaled steroid	Yes vs No	1.4 (0.9 - 2.2)	0.191	0.5 (0.2 – 1.0)	0.165	1.1 (0.7 - 1.8)	0.704	0.8 (0.4 - 1.7)	0.708
Azithromycin	Yes vs No	2.7 (1.9 - 3.8)	<0.001	2.0 (1.0 - 4.1)	0.165	3.3 (2.1 - 5.4)	<0.001	2.5 (1.2 - 5.5)	0.059
DNase	Yes vs No	1.1 (0.7 – 2.0)	0.747	0.6 (0.2 - 1.6)	0.499	1.4 (0.8 - 2.5)	0.395	1.5 (0.6 - 3.7)	0.647
Hypertonic Saline	Yes vs No	0.9 (0.5 - 1.6)	0.883	0.8 (0.3 - 2.4)	0.726	1.1 (0.5 - 2.1)	0.880	0.8 (0.4 - 1.8)	0.742
Pseudomonas aeruginosa	Yes vs No	2.1 (1.5 – 3.0)	<0.001	1.0 (0.5 - 2.3)	0.901	2.6 (1.7 - 3.9)	<0.001	2.3 (1.2 - 4.8)	0.059
Staphylococcus aureus	Yes vs No	0.8 (0.6 - 1.1)	0.180	0.6 (0.2 - 1.4)	0.401	0.7 (0.5 - 1.1)	0.269	0.6 (0.2 - 1.6)	0.592
Burkholderia cepacia complex	Yes vs No	1.0 (0.4 - 2.4)	0.939	1.8 (0.2 - 17.1)	0.716	1.7 (0.7 - 3.8)	0.376	1.0 (0.1 - 8.2)	0.988
MRSA	Yes vs No	1.5 (0.9 - 2.6)	0.191	2.5 (0.6 - 10.2)	0.396	1.3 (0.8 - 2.3)	0.427	Not available	<0.001
Stenotrophomonas maltophilia	Yes vs No	1.6 (1.0 - 2.5)	0.073	1.3 (0.3 – 5.0)	0.726	1.5 (0.8 - 2.8)	0.395	1.3 (0.4 - 4.6)	0.828
Achromobacter species	Yes vs No	2.3 (1.5 - 3.6)	<0.001	2.3 (0.7 - 8.3)	0.396	1.4 (0.7 - 2.9)	0.496	0.4 (0.1 - 3.3)	0.639
Aspergillus colonisation	Yes vs No	1.9 (1.0 - 3.5)	0.068	0.4 (0.0 - 3.5)	0.607	0.8 (0.3 - 1.9)	0.697	1.0 (0.4 - 2.7)	0.988

Abbreviations: ABPA= allergic bronchopulmonary aspergillosis, BMI=body mass index, CFTR=cystic fibrosis transmembrane conductance regulator, GI=gastrointestinal, MRSA= methicillin-resistant *Staphylococcus aureus*, FEV1=percent predicted forced expiratory volume, Iva=ivacaftor, Tez=tezacaftor, Lum=lumacaftor, Elexa=elexacaftor

p-values are adjusted for multiple comparison using False Discovery Rate method.

1 A person was considered underweight if their BMI z score was <-2

Supplementary Table 5 Factors associated with symptoms of SARS-CoV-2 infection in people with cystic fibrosis (mixed effects multivariable logistic regression)

Characteristics of pwCF		**Any symptoms**		**General symptoms**		**Pulmonary symptoms**	
		Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Gender	male vs female	0.8 (0.6 - 1.2)	0.344	1.1 (0.8 - 1.7)	0.521	0.8 (0.7 - 1)	0.086
Age	18-29 vs 0-17 years	1.1 (0.7 - 1.7)	0.677	1.4 (0.9 - 2.3)	0.157	1.7 (1.1 - 2.6)	0.023
	30-39 vs 0-17 years	1.6 (0.9 - 3.0)	0.113	2.0 (1.1 - 3.7)	0.028	2.1 (1.1 - 4.3)	0.035
	40+ vs 0-17 years	2.6 (1.2 - 5.3)	0.010	2.9 (1.6 - 5.2)	<0.001	4.0 (2.0 - 8.1)	<0.001
Genotype	Any F508del vs no F508del	2.1 (1.3 - 3.5)	0.004	1.9 (1.1 - 3.2)	0.018	1.3 (0.9 - 1.9)	0.111
BMI underweight	Yes vs No	0.8 (0.3 - 2.3)	0.743	0.9 (0.4 - 2.5)	0.885	0.8 (0.5 - 1.5)	0.555
Lung function (FEV1 % predicted)	>40-70% vs >70%	1.3 (0.8 - 2.2)	0.233	1.4 (0.8 - 2.3)	0.205	1.3 (0.9 - 1.8)	0.140
	≤40% vs >70%	1.3 (0.7 - 2.4)	0.338	1.3 (0.7 - 2.4)	0.433	1.6 (0.9 - 2.9)	0.091
Pancreatic enzymes	Yes vs No	0.6 (0.4 - 1.0)	0.061	0.5 (0.2 - 0.9)	0.019	0.7 (0.5 - 1.1)	0.162
CF related diabetes	Yes vs No	0.7 (0.5 - 1.2)	0.192	0.9 (0.6 - 1.4)	0.619	0.9 (0.6 - 1.3)	0.550
Lung transplant	Yes vs No	1.1 (0.6 - 2.1)	0.736	1.0 (0.5 - 1.8)	0.916	0.8 (0.5 - 1.1)	0.190
CFTR modulator therapy	Yes vs No	0.8 (0.6 – 1.0)	0.084	0.8 (0.6 - 1.1)	0.199	0.8 (0.6 - 1.2)	0.379
Azithromycin	Yes vs No	0.8 (0.5 - 1.4)	0.493	1.0 (0.6 - 1.6)	0.900	1.4 (0.9 - 2.2)	0.123
Pseudomonas aeruginosa	Yes vs No	1.0 (0.7 - 1.4)	0.790	0.9 (0.6 - 1.3)	0.626	1.1 (0.7 - 1.7)	0.687

Supplementary Table 6 Factors associated with outcomes of SARS-CoV-2 infection in people with cystic fibrosis (mixed effects multivariable logistic regression)

Characteristics of pwCF		**Hospitalization**		**Oxygen therapy**	
		Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Gender	male vs female	0.8 (0.5 - 1.2)	0.241	1.1 (0.7 - 1.8)	0.705
Age	18-29 vs 0-17 years	0.6 (0.4 – 1.0)	0.060	0.4 (0.2 - 0.8)	0.009
	30-39 vs 0-17 years	0.8 (0.4 - 1.7)	0.607	0.7 (0.3 - 1.7)	0.443
	40+ vs 0-17 years	1.3 (0.7 - 2.2)	0.427	0.9 (0.5 - 1.8)	0.795
Genotype	Any F508del vs no F508del	0.9 (0.6 - 1.3)	0.472	0.8 (0.4 - 1.3)	0.298
BMI underweight	Yes vs No	1.9 (0.8 - 4.5)	0.119	0.6 (0.2 - 1.9)	0.398
Lung function (FEV1 % predicted)	>40-70% vs >70%	2.4 (1.6 - 3.6)	<0.001	5.2 (3.2 - 8.4)	<0.001
	≤40% vs >70%	5.4 (2.2 – 13.0)	<0.001	20 (10.7 - 37.5)	<0.001
Pancreatic enzymes	Yes vs No	1.2 (0.8 - 1.8)	0.404	1.2 (0.4 - 3.4)	0.712
CF related diabetes	Yes vs No	1.7 (1.1 - 2.6)	0.027	1.4 (0.9 - 2.3)	0.172
Lung transplant	Yes vs No	3.2 (1.7 - 6.1)	<0.001	3.3 (1.4 - 7.4)	0.005
CFTR modulator therapy	Yes vs No	0.6 (0.4 – 1.0)	0.051	0.8 (0.5 - 1.4)	0.487
Azithromycin	Yes vs No	1.8 (1.1 - 2.9)	0.017	2.4 (1.4 – 4.0)	0.002
Pseudomonas aeruginosa	Yes vs No	1.2 (0.7 - 1.9)	0.485	1.1 (0.7 - 1.8)	0.552

ICU and Respiratory support had too few patients to fit multivariable model (note-univariable models were fitted, Supplementary Tables 2 and 3))