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

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Shareable abstract (@ERSpublications)
In a European study of #SARSCoV2 infection in 828 people with #cysticfibrosis, 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. https://bit.ly/3vPjD2f

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Abstract

Background Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in people with cystic fibrosis (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 December 31, 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) ($p \leqslant 0.001$).

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

Factors associated with hospitalisation and oxygen therapy were lung transplantation, cystic fibrosis-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 1 s <70% predicted, CFRD and those with lung transplants are at particular risk of more severe outcomes.

Introduction

The novel severe acute respiratory syndrome coronavirus 2 (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 (CF) (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 June 30, 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 December 31, 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.

Methods

Study design

The methodology of this prospective observational study has been previously described in a paper presenting data collected between February 1, 2020 and June 30, 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 computed tomography scan, serology or antigen test without PCR confirmation were excluded. Data were reported directly to ECFSPR using a standardised 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 (www.ecfs.eu/projects/ecfs-patient-registry/Variables-Definitions). Per cent predicted forced expiratory volume in 1 s ($ppFEV_1$) 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.

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).

TABLE 1 Symptoms and outcomes of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in people with cystic fibrosis

	Total		Non-lung transplant		Lung transplant	
	n (%)	Missing	n (%)	Missing	n (%)	Missing
Subjects n	828		750		78	
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 and 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						
Hospitalisation	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
Noninvasive 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

Percentages were calculated on total numbers in each group (not on number of symptomatic patients/group). ENT: ear, nose and throat; BIPAP: bilevel positive airway pressure; CPAP: continuous positive airway pressure; ECMO: extracorporeal membrane oxygenation.

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 with 95% confidence intervals 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.

Results

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.

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 (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 and systemic arterial hypertension. Concomitant medications also differed, due to different indications and medical needs.

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 and 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.

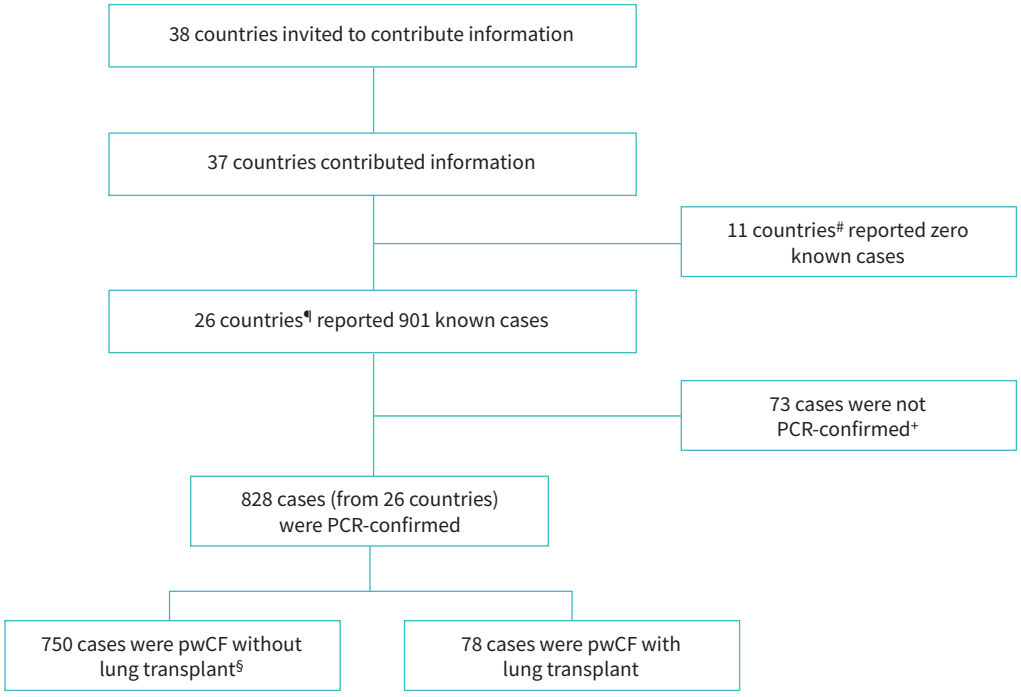

FIGURE 1 Data collection for people with cystic fibrosis (pwCF) and SARS-CoV-2 infection. #: Albania, Belarus, Bulgaria, Cyprus, Georgia, Lithuania, Luxembourg, Republic of Moldova, Romania, Serbia and Ukraine. Hungary did not report information to ECFSPR. ¶: Armenia, Austria, Belgium, Croatia, Czech Republic, Denmark, France, Germany, Greece, Israel, Ireland, Italy, Latvia, Netherlands, Norway, North Macedonia, Portugal, Poland, Russia, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey and UK. +: these cases were diagnosed by antibody test, antigen test, CT scan or medical team opinion without PCR confirmation. §: this group included 10 people with non-lung solid organ transplants (seven liver, two kidney, one unspecified).

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.

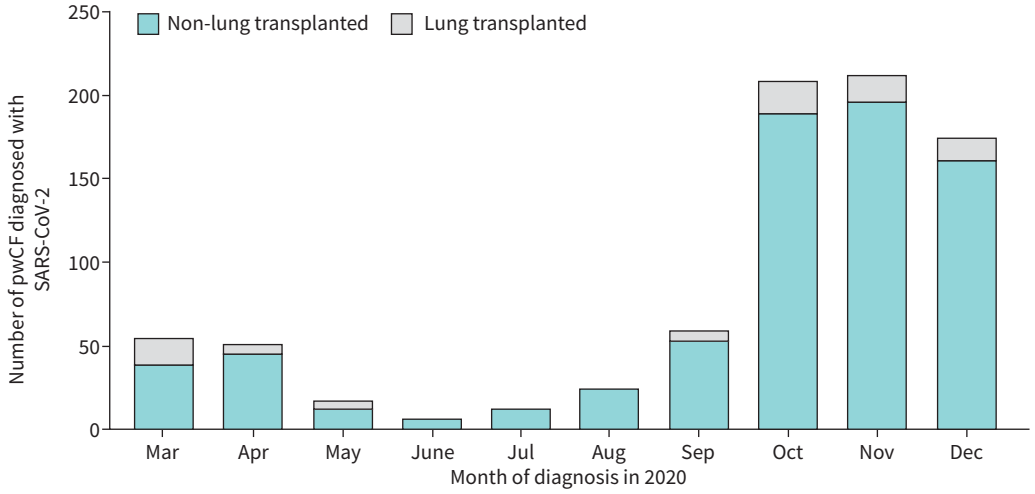

FIGURE 2 Diagnosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in people with cystic fibrosis (pwCF) (n=828) in 2020, by month.

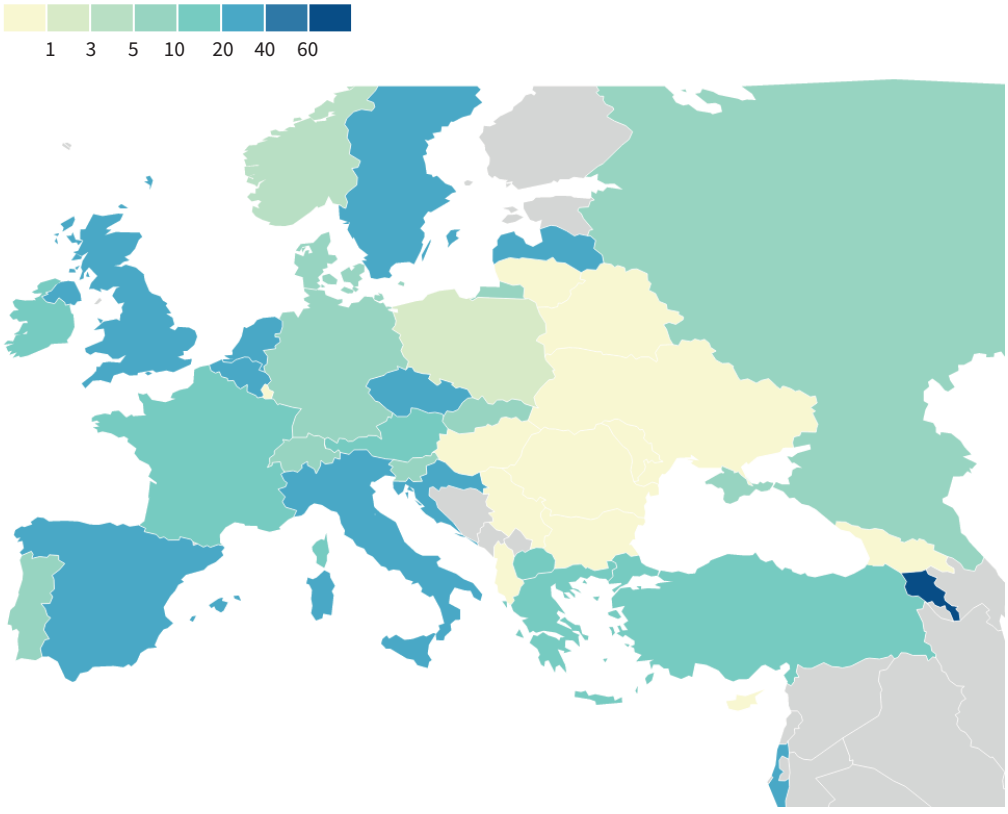

FIGURE 3 SARS-CoV-2 incidence per 1000 people with cystic fibrosis in 2020, by country.

Oxygen therapy, respiratory support and hospitalisation 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 hospitalised patients, intensive care and death were around 2-fold more frequent in lung-transplanted pwCF *versus* non-lung-transplanted pwCF.

Factors associated with symptoms and worse outcomes

Univariable analyses are summarised in figure 4, with full results in supplementary Tables 3 and 4.

TABLE 2 Incidence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection up to 31 December 2020 in people with cystic fibrosis (pwCF) by lung transplant status and by age group

Age group years	All			Non-lung transplant			Lung transplant		
	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	48 211	17.2 (16.0–18.4)	750	45 266	16.6 (15.4–17.8)	78	2729	28.6 (22.7–35.5)
0–11	134	17 179	7.8 (6.5–9.2)	134	17 100	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	12 162	23.9 (21.3–26.8)	268	11 286	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)

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 European Cystic Fibrosis Society Patient Registry report (2017 for France).

TABLE 3 Demographics and pre-infection characteristics of people with cystic fibrosis (CF)

	Total		Non-lung transplant		Lung transplanted[#]	
	n (%)[¶]	Missing	n (%)[¶]	Missing	n (%)[¶]	Missing
Subjects n	828		750		78	
Sex		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[+]		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 FEV_1 % pred[§]		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

CFTR: cystic fibrosis transmembrane conductance regulator; BMI: body mass index; FEV_1 % pred: per cent predicted forced expiratory volume in 1 s; ABPA: allergic bronchopulmonary aspergillosis; GI: gastrointestinal; Iva: ivacaftor; Lum: lumacaftor; Tez: tezacaftor; Elexa: elexacaftor; MRSA: methicillin-resistant *Staphylococcus aureus*. [#]: 10 recipients of other solid organ transplants were included in this group (7 liver, 2 kidney, 1 unspecified). [¶]: percentages are computed excluding missing data. [+]: BMI z-score was only calculated for patients aged 2 years and over, using Centers for Disease Control and Prevention reference values [40]. [§]: FEV_1 % pred was only calculated for patients aged 6 years and over.

	Any symptoms	General symptoms	Gastrointestinal symptoms	Pulmonary symptoms	Hospitalisation	Intensive care	Oxygen therapy	Respiratory support
Male *versus* female					–			
Age 18–29 *versus* <18 years				+				
Age 30–39 *versus* <18 years		+						
Age >40 *versus* <18 years		+		+	+		+	+
Any F508del *versus* no F508del								
Low BMI (z-score <-2)					+		+	
FEV_1 % pred 41–70% *versus* >70%					+		+	+
FEV_1 ≤40% *versus* >70%					+		+	+
Pancreatic insufficiency		–			+			
CF-related diabetes					+	+	+	+
Lung transplant					+	+	+	+
ABPA					+			
Chronic liver GI disease								
Arterial hypertension					+		+	
CFTR modulators								
Inhaled antibiotics					+		+	+
Oral antibiotics					+			
Inhaled steroids								
Azithromycin					+		+	
DNAse								
Hypertonic saline								
Pseudomonas aeruginosa					+		+	
Staphylococcus aureus								
Burkholderia cepacia complex								
MRSA								
Stenotrophomonas maltophilia								
Achromobacter species					+			
Aspergillus colonisation								

FIGURE 4 Factors positively (+) and negatively (–) associated with SARS-CoV-2 infection symptoms and outcomes. ABPA: allergic bronchopulmonary aspergillosis; BMI: body mass index; CFTR: cystic fibrosis transmembrane conductance regulator; GI: gastrointestinal; MRSA: methicillin-resistant *Staphylococcus aureus*; FEV_1 % pred: per cent predicted forced expiratory volume in 1 s. A person was considered underweight if their BMI z-score was ⩽2, using Centers for Disease Control and Prevention reference values [40].

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 cystic fibrosis transmembrane conductance regulator (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, nine out of 11 pwCF who died and had complete information available had at least one risk factor for hospitalisation and/or oxygen therapy (information was incomplete for two adult pwCF).

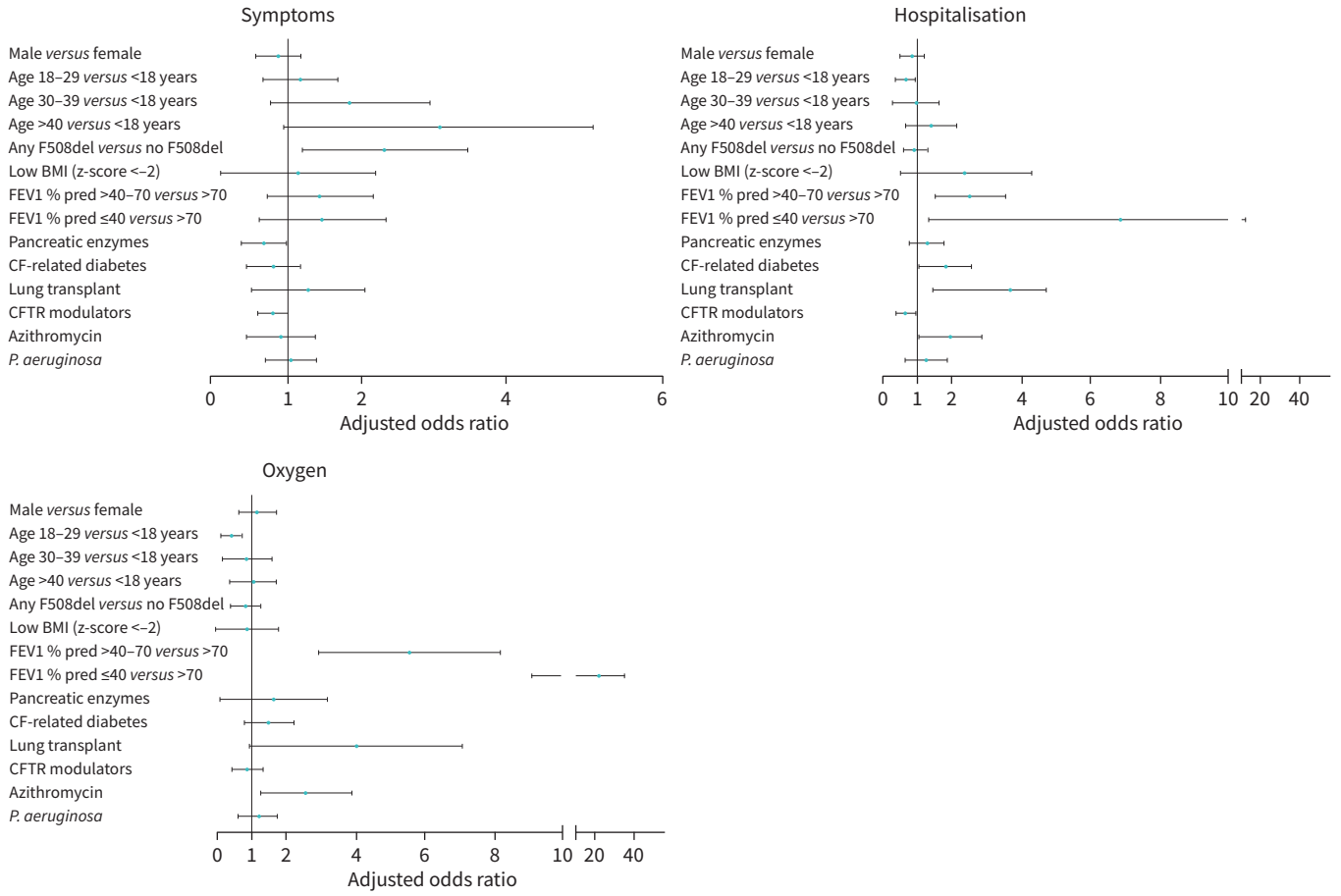

FIGURE 5 Multivariable analysis of factors associated with symptoms and outcomes of SARS-CoV-2 infection in people with cystic fibrosis (CF). BMI: body mass index; CFTR: cystic fibrosis transmembrane conductance regulator; FEV_1 % pred: per cent predicted forced expiratory volume in 1 s; *P. aeruginosa*: *Pseudomonas aeruginosa*.

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 December 31, 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 June 30, 2020 [7] to 1.4% up to December 31, 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 coronavirus disease 2019 (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 an 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 to 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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