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Original Article

A multinational report on SARS-COV-2 infection outcomes in people with CF and *Aspergillus* infection or ABPA

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ABSTRACT

Background: *Aspergillus* infection is known to be associated with worse respiratory outcomes in people with CF (pwCF) and is a well-recognised complication of severe SARS-CoV-2 infection. The aim of this observational cross-sectional study was to examine the association of pre-existing *Aspergillus* infection and/or allergic bronchopulmonary aspergillosis (ABPA) in pwCF and severity of COVID-19.

Methods: Data on SARS-CoV-2 infections in pwCF from January 2020 to June 2021 were collected by the European Cystic Fibrosis Society Patient Registry. The primary outcome was COVID-19 severity measured by hospitalisation comparing those with *Aspergillus* infection and/or ABPA in the 12 months preceding COVID-19and those without.

Results: In total, 1095 pwCF were diagnosed with SARS-CoV-2 and information on pre-existing *Aspergillus*/ABPA status was available from 807. PwCF and SARS-CoV-2 in the *Aspergillus*/ABPA group (n = 153), in comparison to the non-*Aspergillus*/ABPA group (n = 654), were more likely to be hospitalised (adjusted OR 1.79 (1.19 to 2.85); p = 0.005) and their disease course was more likely to be complicated by sepsis (adjusted OR 7.78 (1.78 to 49.43); p = 0.008). The association with hospital admission was no longer significant after excluding patients with ABPA. Secondary analysis comparing pwCF who received antifungal treatment (n = 18), versus those who did not (n = 474) during COVID-19, showed a higher rate of hospitalisation ($p < 0.001$); intensive care unit admission ($p < 0.001$), and requirement for invasive ventilation ($p < 0.001$) in the antifungal treated group.

Conclusion: We show that pre-existing *Aspergillus*/ABPAis associated with increased rates of hospitalisation and sepsis during COVID-19 in pwCF.

1. Introduction

Patients with severe pneumonia caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) are susceptible to fungal co-infections, in particular pulmonary aspergillosis [1]. Coronavirus disease 2019 (COVID-19) associated pulmonary aspergillosis (CAPA) has been shown to significantly impact the outcomes of patients admitted to the ICU, with increased length of hospital stay and increased mortality rates compared to those without *Aspergillus* co-infection [1–3]. A qualitative review including 21 observational studies with mortality data (n = 3777), showed a mortality rate of 46.2 % in CAPA patients (n = 539) versus 31.3 % in the non-CAPA group ($n = 3238$) ($p < 0.001$) [1]. Over 600 cases of proven or probable CAPA have been reported in patients with COVID-19, reflecting an incidence rate of 10.9 % [1]. Only scarce data is available on the impact of antifungal therapy on survival in CAPA patients, but no significant difference was found in survival in those specifically treated for CAPA and those who were not [1,2,4].

People with CF (pwCF) were assumed to be highly vulnerable to SARS-CoV-2 from early on in the COVID-19 pandemic, and therefore most countries advised 'shielding' to minimise the risk for infection.

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Previous studies using data from the European Cystic Fibrosis Society Patient Registry (ECFSPR) have shown that SARS-CoV-2 infection has worse outcomes in pwCF compared to the general population of the same age in terms of increased morbidity and hospitalisation [5,6].

Infection and disease caused by *Aspergillus* spp. is a common complication in pwCF and is observed in up to 60 % of adult patients [7]. Allergic responses to *Aspergillus* spp., presenting as allergic bronchopulmonary aspergillosis (ABPA), have shown to worsen long-term outcomes [8–10]. The impact of non-allergic *Aspergillus* infection on lung function is less clear, but some recent studies have shown that *Aspergillus* infection in pwCF is associated with lung function decline and structural lung damage [11–13].

It is likely that pwCF who are already colonised with *Aspergillus* will be more susceptible to CAPA during SARS-CoV-2 infection and may therefore experience worse COVID-19 outcomes. We used prospectively collected data from the ECFSPR during the COVID-19 pandemic to determine the relationship between pre-existing *Aspergillus* infection and/or ABPA and COVID-19 outcomes in pwCF.

2. Methods

2.1. Study design and study population

This cohort study was conducted using anonymised data on pwCF, who had SARS-CoV-2 infection (positive PCR test) between 1st January 2020 and 30th June 2021, from the countries who participated in the European Cystic Fibrosis Society Patient Registry (ECFSPR) COVID-19 data collection (see Supplemental file). Anonymised patient data was provided from 2 time points: data on clinical characteristics and outcomes after SARS-CoV-2 infection; and data from these patients' annual review in the year preceding SARS-CoV-2 infection, with information on demographics and CF disease characteristics. The ECFSPR (www.ecfs.eu/ecfspr) is a patient registry which collects demographic and clinical data from consenting pwCF in Europe and neighbouring countries and is subject to local ethical approval and data governance [14]. PwCF who contribute data do so with informed consent and the retrieval of data for research is to be approved by each country separately [15].

The primary outcome of this study was hospitalisation for COVID-19 and the secondary outcomes were mortality, Intensive Care Unit (ICU) admission, oxygen and ventilation requirement, and COVID-19 related complications. Variables were defined where possible according to ECFSPR standards (www.ecfs.eu/projects/ecfs-patient-registry/Variables-Definitions). Specifically, *Aspergillus* infection was defined as a positive microbiology sample at least once as reported in the previous annual review data. A diagnosis of ABPA was up to the treating physician providing the data.

The total number of patients were grouped based on the presence or absence of *Aspergillus* infection and/or ABPA in the preceding 12 months of the SARS-CoV-2 infection. The aim was to assess whether pre-existing *Aspergillus* infection and/or ABPA in pwCF is associated with more severe COVID-19. As a secondary analysis, the cohort was grouped by whether the patients received antifungal treatment during COVID-19 to assess the association between antifungal treatment during COVID-19 and disease severity.

2.2. Statistical analysis

Characteristics of pwCF before SARS-CoV-2 infection, with and without *Aspergillus* infection or ABPA, were summarized using descriptive statistics. Missing data in the groups are specified in the tables if exceeding 10 %. Fisher exact test and Wilcoxon test were used to compare values of categorical and numerical variables respectively between the two groups. Logistic regression models were used to assess the association between pre-existing *Aspergillus* infection and/or ABPA and COVID-19 severity, complications, and outcomes. Where numbers allowed the models were adjusted for age at SARS-CoV-2 infection, value of FEV_1 percent of predicted ($ppFEV_1$), and lung transplant status. Two sensitivity analyses were undertaken to ensure the validity of the main study results. The first after exclusion of lung transplant recipients, and the second after exclusion of ABPA patients. All results are presented as adjusted odds ratios (OR) with 95 % confidence intervals (CI) and p-values. P-values were considered significant when < 0.05.

For the secondary analysis pwCF and SARS-CoV-2 were grouped according to who received antifungal treatment and descriptive analysis was completed with the same methods. A sensitivity analysis was undertaken on the non-transplant cohort. Logistic regression models were used to measure the association between antifungal treatment and COVID-19 severity, complications, and outcomes. Each model was fitted only if at least 5 events for each explanatory variable were available. Results are presented as odds ratios (OR) with 95 % confidence intervals (CI) and p-values. P-values were considered significant when < 0.05.

The statistical analyses were performed using SAS, version 9.4, (SAS Institute Inc., Cary, NC, USA) and R software, version 4.2.2.

3. Results

3.1. Study population

1095 pwCF were diagnosed with a SARS-CoV-2 infection between January 2020 and June 2021. Information was available on the presence or absence of *Aspergillus* infection or ABPA in the preceding 12 months for 807 pwCF (73.7 %), and these cases were included in the study. *Aspergillus* infection or ABPA was present in 153 (19.0 %) in the preceding 12 months before SARS-CoV-2 infection (table 1). Of these 11 had both ABPA and *Aspergillus* infection, 115 had *Aspergillus* infection only, and 27 had ABPA only. Overall, the median age of the study participants was 23 years (range 0.25 – 83 years) and 412 (51.1 %) were female. Eighty (11.6 %) participants had a $ppFEV_1$ below 40 %, 322 (46.7 %) between 40 % and 80 % and 287 (41.7 %) over 80 %. Seventy-six (9.4 %) had received a lung transplant, and 190 (26.3 %) were on CFTR modulator therapy.

3.2. Baseline (pre-COVID-19) characteristics of Aspergillus/ABPA group and non-Aspergillus/ABPA group

The *Aspergillus*/ABPA group was older than the non-*Aspergillus*/ABPA group, median age 25 versus 21.3 years, respectively ($p < 0.001$). The proportion of those with ppFEV1 < 40 was similar in the 2 groups (11.7 % versus 11.5 %). The *Aspergillus*/ABPA group had a higher proportion of patients with ppFEV1 40–80, 53.4 % versus 44.9 %, but overall lung function was not significantly different between the 2 groups. There was no significant difference in BMI z-scores ($p = 0.24$), genotype ($p = 0.14$), and the number of pwCF who had received a lung transplant ($p = 0.54$) between the two groups. The prevalence of CF-related diabetes (CFRD) was significantly higher in the Aspergillus/ABPA group (30.2 % versus 21.0 %, $p = 0.02$).

The *Aspergillus*/ABPA group had significantly higher rates of co-infection with *Pseudomonas aeruginosa* ($p = 0.008$) and non-tuberculous mycobacteria (NTM) ($p = 0.01$) (Table 1). Infection rates with *Staphylococcus aureus* and *Burkholderia cepacia* did not differ significantly between the two groups.

Oral azithromycin, inhaled antibiotics and inhaled steroids were significantly more commonly used during the 12 months prior to SARS-CoV-2 infection in the *Aspergillus*/ABPA group (table 1). Oral antibiotics, other than azithromycin, and oral steroids did not differ significantly between the two groups. Previous treatment with non-steroidal anti-inflammatory medication (NSAIDs) was significantly less common in the *Aspergillus*/ABPA group versus the non-*Aspergillus*/ABPA group ($p < 0.001$).

Categorical variables: Numbers (%). Continuous variables given in ranges: Numbers (%). BMI z scores interquartile ranges and minimum/maximum given. *If missing data is $\geq$ 10 % for specific variable, total

Table 1
Baseline (pre-COVID-19) characteristics of people with Cystic Fibrosis included in the study.

	Total N = 807 (%)	Non-*Aspergillus*/ ABPA group N = 654 (%)	*Aspergillus*/ ABPA group N = 153 (%)	p-value
Sex				
Male	395 (48.95)	314 (48.01)	81 (52.94)	0.282
Female	412 (51.05)	340 (51.99)	72 (47.06)	
Age class				
0–11 years	166 (20.57)	157 (24.01)	9 (5.88)	< 0.001
12–17 years	120 (14.87)	97 (14.83)	23 (15.03)	
18–29 years	264 (32.71)	199 (30.43)	65 (42.48)	
30–39 years	139 (17.22)	105 (16.06)	34 (22.22)	
40–49 years	88 (10.90)	70 (10.70)	18 (11.76)	
50+ years	30 (3.72)	26 (3.98)	4 (2.61)	
BMI z-score (median, range)				
Min	−30.5	−30.2	−4.5	0.242
Q1	−1.0	−1	−1	
Q2	−0.2	−0.2	−0.3	
Q3	0.5	0.5	0.3	
Max	2.5	2.5	2	
Underweight (z-score <−2)	57 (7.44)	45 (7.28)	12 (8.11)	0.728
Genotype				
ΔF508 Homozygous	271 (33.58)	209 (31.96)	62 (40.52)	0.138
ΔF508 Heterozygous	337 (41.76)	279 (42.66)	58 (37.91)	
Other	199 (24.66)	166 (25.38)	33 (21.57)	
ppFEV1				
> 80	287 (41.65)	235 (43.44)	52 (35.14)	0.159
40–80	322 (46.73)	243 (44.92)	79 (53.38)	
< 40	80 (11.61)	63 (11.65)	17 (11.49)	
CF related diabetes	170 (22.64)	129 (20.98)	41 (30.15)	0.024
CFTR Modulator Use	190 (26.32)	151 (26.03)	39 (27.47)	0.750
Lung Tx	76 (9.42)	64 (7.93)	12 (1.49)	0.540
Oxygen therapy pre-COVID				
Oxygen	24 (4.95)	23 (5.41)	1 (1.67)	0.346
NIPPV*	9/483 (1.86)	9/423 (2.13)	0/60 (0.00)	0.610
Antibiotic therapy pre-COVID				
Oral (excluding Azithromycin)*	134/548 (24.45)	109/461 (23.64)	25/87 (28.74)	0.341
Inhalation*	281/638 (44.04)	216/538 (40.15)	65/100 (65.00)	< 0.001
Azithromycin	285 (35.58)	208 (31.95)	77 (51.33)	< 0.001
Pre-COVID treatments				
Oral steroids*	45/408 (11.03)	40/359 (11.14)	5/49 (10.20)	1.000
Inhaled steroids	305 (38.85)	223 (34.90)	82 (56.16)	< 0.001
NSAID	402 (55.22)	354 (60.21)	48 (33.37)	< 0.001
Other immunosuppressive therapy*	30/411 (7.30)	29/361(8.03)	1/50 (2.00)	0.154
Pre-COVID infections				
S. aureus	493 (65.91)	388 (64.56)	105 (71.43)	0.121
*B. cepacia**	32/685 (4.67)	27 (4.73)	5/114 (4.39)	1.000
P. aeruginosa	355 (46.04)	272 (43.66)	83 (56.08)	0.008
NTM*	8/471 (1.70)	4/412 (0.97)	4/59 (6.78)	0.011

number is specified. BMI; body mass index, $ppFEV_1$; percentage predicted Forced Expiratory Volume in 1 s, CFTR; cystic fibrosis transmembrane conductance regulator, Tx; transplantation; NIPPV; non-invasive positive pressure ventilation, NSAID: non-steroidal anti-inflammatory drug, NTM; non-tuberculous mycobacteria.

3.3. *Aspergillus* infection or ABPA and COVID-19 disease severity

i) COVID-19 Severity Outcomes

PwCF in the *Aspergillus*/ABPA group were significantly more likely to be hospitalised with COVID-19 compared to the non-*Aspergillus*/ABPA group (32.0 % versus 20.8 % (OR 1.79 (1.19–2.85); p = 0.005)). There were similar rates of ICU admissions, oxygen requirement, non-invasive ventilation and invasive ventilation. Covid-19 associated mortality was low and no significant difference was observed between the two groups (table 2).

*ii) Treatments during SARS-CoV-2 infection*There was significantly higher use of antifungals in the *Aspergillus*/ABPA group versus non-*Aspergillus*/ABPA group (8.5 % versus 2.8 % (OR 3.21 (1.26 to 15.91); p = 0.016). The use of other treatments such as antiviral therapy, antibiotic therapy and systemic steroids did not differ significantly between the two groups.

*iii) Complications of COVID-19*There was a significant association of sepsis during COVID-19 in the *Aspergillus*/ABPA group, versus non-*Aspergillus*/ABPA group (6.9 % versus 0.9 % (adjusted OR 7.78 (1.78 to 49.43); p = 0.008). However, numbers were small with only 4 cases of sepsis in each group (table 2). Occurrence of CF pulmonary exacerbations and bacterial pneumonia was comparable in both groups. Multi-organ failure was rare in both groups. Acute respiratory distress syndrome (ARDS) was rare and was observed in 7 patients in the non-*Aspergillus*/ABPA group only.

*iv) Sensitivity analyses.*The sensitivity analysis in the non-transplant group showed that the baseline characteristics of pwCF with or without *Aspergillus*/ABPA were comparable to the total cohort, and that the associations between preceding *Aspergillus* infection and/or ABPA and hospitalisation (adjusted OR 1.69 (1.03 to 2.63); p = 0.035) and sepsis (adjusted OR 5.55 (0.96 to 32.26); p = 0.045) remain significantly different, with a higher use of antifungals (7.0 % versus 1.7 %; p = 0.03) during COVID-19 (Supplemental Table 1–2). In contrast, excluding pwCF and ABPA from the cohort showed that the prevalence of CFRD and pre-COVID-19 infection with *P. aeruginosa* was no longer significantly different between the group with or without preceding *Aspergillus* infection. No significant impact of previous *Aspergillus* infection in pwCF on COVID-19 associated hospitalisation (p = 0.084) and antifungal use (p = 0.05) was observed (Supplemental Table 3–4). The development of sepsis (6.9 % versus 0.9 %; p = 0.006) remained significantly higher in the *Aspergillus* infection group.

All variables: Numbers (%). *If missing data is ≥ 10 % for specific variable, total number is specified. [&]Odds ratio with 95 % confidence

Table 2
Characteristics of COVID-19 in patients with Cystic Fibrosis in the presence or absence of *Aspergillus* infection or ABPA.

	Total N = 807 (%)	Non-*Aspergillus* / ABPA group N = 654 (%)	*Aspergillus* /ABPA group N = 153 (%)	Adjusted[&] OR (95 % CI)	Adjusted[&] p-value[1]
COVID Severity Outcomes					
Community treated	612 (77.08)	510 (79.19)	102 (68.00)	0.56(0.35 - 0.84)	0.005
Hospital admission	182 (22.92)	134 (20.81)	48 (32.00)	1.79(1.19 - 2.85)	0.005
ICU admission	30 (3.72)	26 (3.98)	4 (2.61)	0.65(0.20 - 1.96)	0.534
Oxygen requirement	92 (11.54)	77 (11.96)	15 (9.80)	0.80(0.34 - 1.23)	0.214
Non-invasive ventilation	23 (3.11)	18 (2.80)	5(3.27)	1.25(0.34 - 2.92)	0.876
Invasive ventilation	17 (2.30)	13 (2.16)	4 (2.96)	1.39(0.39 - 4.80)	0.521
Death	13 (1.61)	10 (1.53)	3 (1.95)	1.29(0.30 - 5.38)	0.619
Treatment during COVID infection					
Antiviral therapy*	32/485 (6.60)	31/426 (7.28)	1/59(1.70)	n.a.	n.a.
Antibiotic therapy (oral & IV)*	355/711 (49.93)	285/584(48.8)	70 (55.12)	1.29(0.84 – 1.90)	0.266
Systemic Steroids*	125/701 (17.83)	96 (16.64)	29 (23.39)	1.53(0.80 – 2.20)	0.250
Hydroxychloroquine*	16/487 (3.29)	12/428 (2.80)	4/59 (6.78)	2.52(0.65 – 7.85)	0.146
Vitamin C*	50/486 (10.29)	47/427 (11.01)	3/59 (5.09)	0.43(0.08 – 1.06)	0.103
Immunomodulators*	5/419 (1.19)	4/370 (1.08 %)	1/49 (2.04)	n.a.	n.a.
Antifungal therapy*	17/487 (3.49)	12/428 (2.80)	5/59 (8.48)	3.21(1.26 – 15.91)	0.016
Complications of COVID					
Sepsis*	8/482 (1.66)	4/424 (0.94)	4/58 (6.90)	7.78(1.78 – 49.43)	0.008
Multiorgan failure	5 (0.62)	4 (0.61)	1 (0.66)	n.a.	n.a.
CF pulmonary exacerbation*	103/806 (14.65)	78/653 (11.95)	25/153 (16.34)	1.62(0.84 – 2.43)	0.167
ARDS*	7/480 (1.46)	7/422 (1.66)	0/59 (0.0)	n.a.	n.a.
Bacterial Pneumonia*	14/480 (2.92)	11/422 (2.61)	3/58 (5.17)	2.04(0.45 – 8.02) –	0.282

interval and p-value$_1$ adjusted for age at SARS-CoV-2 infection, pre-infection value of percentage predicted FEV_1, status of lung transplant. ICU; intensive care unit, ARDS; acute respiratory distress syndrome. N.a; not applicable.

3.4. Antifungal treatment during SARS-CoV-2 infection and severity of COVID-19 disease

Of the 1095 pwCF and SARS-CoV-2 infection, data on antifungal treatment was recorded in 492 (45.0 %), and 18 (3.7 %) received antifungal treatment during SARS-CoV-2 infection (Supplementary Table 5). . There were no significant differences between these 2 groups with respect to gender, age, BMI, lung function, genotype and *Aspergillus* infection or ABPA in the preceding year. Those having had a lung transplant were 11 times more likely to be treated with antifungals during COVID-19 (38.9 % versus 5.5 %; $p < 0.001$). Oral antimicrobial and immunomodulatory treatments prior to COVID-19 were significantly associated with receiving antifungal treatment during COVID-19.

COVID-19 outcomes were much worse in pwCF who received antifungal treatment during COVID-19, compared to those who did not (Supplementary Table 6). This is shown by a significantly increased rates of hospitalisation, (83.3 % versus 17.4 %; $p < 0.001$), ICU admission (33.3 % versus 2.3 %; $p < 0.001$), oxygen requirement (55.6 % versus 9.8 %; $p < 0.001$), invasive ventilation (22.2 % versus 1.5 %; $p < 0.001$) and mortality (16.7 % versus 1.3 %; $p < 0.001$). In addition, the complications of sepsis (16.7 % versus 0.9 %; $p < 0.001$) and ARDS (22.2 % versus 0.6 %; $p < 0.001$) were much more frequent in the antifungal treated group PwCF who received antifungals, were significantly more likely to be treated with antivirals, antibiotics and steroids

Sensitivity analysis by excluding the lung transplant patients showed that the baseline characteristics of pwCF treated antifungals during COVID-19 were comparable to those not having received antifungal. The significant associations between treatment with antifungals during COVID-19 and hospitalisation ($p < 0.001$), ICU admission ($p = 0.005$), oxygen requirement ($p < 0.001$), development of sepsis ($p = 0.001$) or ARDS ($p < 0.001$), and mortality ($p = 0.001$) remained in non-transplant cohort.

4. Discussion

This study aimed to evaluate the impact of *Aspergillus* infection and ABPA combined on COVID-19 outcomes in pwCF. Although their immunopathogenesis differs, they represent different disease phenotypes caused by *Aspergillus* spp. Our results show a significant association between pre-existing *Aspergillus* infection and ABPA in pwCF and COVID-19 disease severity reflected in increased rates of hospitalisation and sepsis; but no association with other markers of COVID-19 disease severity such as ICU admission and oxygen requirement. The sensitivity analysis, after excluding patients with ABPA, showed that the increased rate of hospitalisation was largely driven by pre-existing ABPA. The development of sepsis remained significantly higher in the *Aspergillus* group after excluding ABPA. Separate analyses on pwCF with ABPA only were not performed due to the low numbers (n = 27) in this group.

Our observations confirm and extend the results from an earlier ESCFSPR study assessing outcomes of COVID-19 in pwCF showing that ABPA was associated with hospitalisation [6]. ABPA as a risk factor for more severe COVID-19 was unfortunately not included in the multivariable model in that study due to > 10 % missing data for this variable [6]. A French CF Registry study showed that pwCF with pre-existing ABPA were significantly more likely to be diagnosed with SARS-CoV-2 infection, but pre-existing ABPA was not associated with worse COVID-19 outcomes [16]. A global study assessing the characteristics and outcomes of COVID-19 in 105 children with CF, showed that ABPA was positively associated with hospitalisation, with five out of 8 children (63 %) with ABPA and COVID-19 needing hospitalisation [17].

To assess the role of pre-existent *Aspergillus*/ABPA more precisely on COVID-19 outcomes, we adjusted our analyses for the factors known to be associated with worse outcomes shown in earlier studies. Age at SARS-CoV-2 infection, pre-infection value of $ppFEV_1$, and lung transplant status have been shown to be associated with worse outcomes of SARS-CoV-2 infection in pwCF [6,18–21]; as well as worse outcomes of COVID-19 in the non-CF population [22–24]. The pwCF in the *Aspergillus*/ABPA group were older than the non-*Aspergillus*/ABPA group as anticipated, as rates of *Aspergillus* infection and ABPA increase with age

in pwCF [25]. These differences remained when patients with ABPA were excluded. There were no significant differences between the groups at baseline in terms of lung function or lung transplant status. Our results show that after adjustment for known confounders, pre-existing *Aspergillus*/ABPA remain associated with worse outcomes of COVID-19 in pwCF. The statistical significance of the association with hospital admission was lost when focussing on *Aspergillus* infection only, although a higher number of pwCF and *Aspergillus* infection were hospitalised (27.4 % versus 20.8 %), but development of sepsis remained significantly higher in the *Aspergillus* infection only group (6.9 % versus 0.9 %; $p = 0.006$) during COVID-19. An explanation for this might be the absence of a clear definition for *Aspergillus* infection, and how to differentiate infection from colonisation. As the total number of respiratory samples positive for *Aspergillus*/year is not captured by the ECFSPR, it was not possible to differentiate between a 'one off' positive sample and persistent (≥ 2) positive samples per year. Furthermore, the type of respiratory sample from which *Aspergillus* was cultured is not captured, with sensitivity and specificity varying between sputum, cough, throat and bronchoalveolar lavage samples [26]. In addition, it is likely the culture techniques vary across the participating countries, with high-volume cultures being more sensitive than standard culture based-techniques in detecting *Aspergillus* [26].

As previous data have indicated that lung transplant is an independent risk factor for more severe COVID-19 [18], we performed a sensitivity analysis by excluding patients who received a lung transplant, but did had no effect on the significant associations found with respect to hospitalisation and development of sepsis during COVID-19.

When taking into account surrogate markers of CF disease severity including CFRD, *P. aeruginosa* infection, NTM infection, the use of inhaled antibiotics, inhaled steroids and azithromycin, significant differences were observed at baseline between the *Aspergillus*/ABPA group, which remained significantly different when either excluding patients with ABPA (with exception of CFRD and *P. aeruginosa* infection) and those who had a received a lung transplant.

In our study, 51.3 % of the *Aspergillus*/ABPA group versus 32.0 % of the non-*Aspergillus*/ABPA group ($p < 0.001$) received chronic azithromycin therapy before SARS-CoV-2 infection. Observational studies have shown an association between azithromycin and *Aspergillus* colonisation in pwCF which authors argue could be due to the anti-inflammatory effect of azithromycin pre-disposing to *Aspergillus* infection CF [27,28]. Jung et al. [6] identified that in pwCF and COVID-19, chronic azithromycin treatment, after adjustment for confounders, was as a risk factor for hospitalisation ($p = 0.02$) and oxygen therapy ($p = 0.002$). Colombo [19] also identified it as a risk factor for hospitalisation after adjustment for age and pancreatic insufficiency ($p = 0.0009$). It is likely that chronic azithromycin therapy is indicative of recurrent bacterial infections, particularly chronic *P. aeruginosa*, thus is a surrogate marker for worse lung disease in pwCF. This is supported by the findings in our study of an association between *Aspergillus*/ABPA and chronic inhaled antibiotic therapy ($p < 0.001$), which remained a significant finding after excluding patients with ABPA or lung transplant. In our study lung function was included as a predictor in the multivariable model, thus precluding the inclusion of azithromycin due to lack of independence from lung function..

In this study 30.2 % of the *Aspergillus*/ ABPA group versus 21.0 % of the non-*Aspergillus*/ABPA group had CF related diabetes (CFRD) ($p = 0.024$). CF registry studies from France [16] Italy [19] Europe [6] and worldwide [18] have shown association between CFRD and more severe COVID-19 outcomes. In the non-CF population, type 1 and 2 diabetes is an important risk factor for COVID-19 mortality as shown in a meta-analysis of 42 global studies [24], and in a meta-analysis of 88 European cohort studies [23]. CFRD differs from diabetes in the non-CF population in that it is not associated with macrovascular complications in the same way, nor obesity, both of which are associated with worse COVID 19 outcomes [23,24]. However, the common features of hyperglycaemia causing impaired immunity; and immune dysregulation impacting response to SARS-CoV-2 are likely to be important in CFRD, as well as non-CF diabetes. In addition, CFRD is a marker of disease severity in pwCF, which develops as the disease progresses, which may also account for the association shown with *Aspergillus*/ ABPA.

The secondary analysis comparing pwCF treated with antifungals, to those not treated with antifungals during COVID-19, shows that antifungal treatment is positively associated with disease severity and increased rates of mortality (16.7 % versus 1.3 %), hospitalisation, ICU admission, oxygen therapy, non-invasive ventilation, ARDS and bacterial pneumonia in the antifungal group. These association remained significant when focussing on the non-transplant cohort only. Antifungal treatment administered to pwCF during COVID-19 is clearly associated with clinical markers of disease severity of both CF and COVID-19 as well as higher mortality compared to those who did not receive antifungals. Our observation reflects the clinical guidance in which antifungal treatment is reserved for severe COVID-19 in ICU patients [29, 30] and may therefore not represent a causative factor, but rather confounding. Pre-existent *Aspergillus*/ABPA was not associated with the administration of antifungals during COVID-19 treatment, as only 9.4 % (6/64) with pre-existent *Aspergillus* infection or ABPA were treated with antifungals. Unfortunately, our study was limited by lack of information available on CAPA, and how this might have impacted antifungal treatment and outcome.

There are several limitations to this study. Firstly, not all countries participating in the ECFSPR participated in the COVID-19 data collection, which might have introduced a bias. Furthermore, the high proportion of missing data > 10 % for certain variables, such as sepsis as a complication of COVID-19 (missing data as specified in all tables with an asterix), is a potential source of bias. In addition, annual review data on antifungal treatment prescribed prior to SARS-CoV-2 infection was not available.

This European observational cohort study is the first to consider the specific importance of pre-existing *Aspergillus* infection and ABPA, on outcomes of COVID-19 in pwCF. The strong association shown between pre-existing *Aspergillus*/ABPA, but not *Aspergillus* infection only, and hospitalisation from COVID-19 is likely due to a combination of the detrimental impact of *Aspergillus*/ABPA on CF lung disease before SARS-CoV-2 infection; the immunological impact of *Aspergillus*-SARS-CoV-2 co-infection; as well as the association of *Aspergillus*/ABPA with other markers of CF disease severity, including CFRD and chronic inhaled antibiotics and azithromycin treatment. Whilst this study shows an association of pre-existing *Aspergillus*/ABPA and sepsis in COVID-19, no association was shown with ICU admission or oxygen or ventilation requirements. In conclusion this study highlights the importance of *Aspergillus*/ABPA in pwCF, showing it to be an important risk factor for disease severity in COVID-19.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2023.10.017.

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