Cumulative Incidence and Risk Factors for Severe COVID-19 in French People with Cystic Fibrosis

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Running title: Severe COVID-19 in Cystic Fibrosis

Abstract

Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections are closely monitored in people with cystic fibrosis (pwCF), with a special emphasis on severe cases. Previous studies used hospitalization rates as proxy for severity.

Methods: We evaluated data from coronavirus disease 2019 (COVID-19) cases diagnosed in French pwCF followed in one of the 47 French CF center over the first year of the pandemic. Objective criteria were applied for defining severity (e.g., respiratory failure and/or death). Data were compared to those from all French pwCF using the French CF Registry.

Results: As of April 30, 2021, 223 pwCF were diagnosed with COVID-19, with higher risks in adults (≥18 years, odds ratio [OR]=2.52, 95% confidence interval [CI]=1.82-3.48) and post-transplant individuals (OR=2.68, 95% CI=1.98-3.63). Sixty (26.9%) patients were hospitalized, with an increased risk in post-transplant individuals (OR=4.74, 95% CI=2.49-9.02). In 34 (15%) cases, COVID-19 was considered severe; 28/60 (46.7%) hospitalizations occurred in patients without objective criteria of severity. Severe cases occurred mostly in adults (85.3%) and post-transplant pwCF (61.8%, OR=6.02, 95% CI=2.77-13.06). In non-transplanted pwCF, risk factors for severity included low lung function (median ppFEV$_1$ 54.6% *vs.* 75.1%, OR=1.04, 95% CI=1.01-1.08) and CF-associated diabetes (OR=3.26, 95% CI=1.02-10.4). While most cases recovered without sequelae (n=204, 91.5%), 16 (13%) were followed for possible sequelae, and three post-transplant females died.

Conclusions: Severe COVID-19 cases occurred infrequently during the first year of the pandemic in French pwCF. Non-transplanted adults with severe respiratory disease or diabetes and post-transplant individuals were at risk for severe COVID-19. Thus, specific preventive measures should be proposed.

Keywords: COVID-19; SARS-CoV-2; cystic fibrosis; risk factors; severity

Introduction

Since its inception in December 2019, the coronavirus disease 2019 (COVID-19) outbreak has changed health concerns and priorities throughout the world. As of January 13, 2022, more than 307 million people had been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and at least 5.49 million individuals have died of this disease worldwide [1]. Cystic fibrosis (CF) affects approximately 7,500 people in France [2] as well as at least 90,000 people worldwide. Lung disease remains the major cause of morbidity and mortality in people with CF (pwCF), with a progressive decline in lung function due to a vicious self-perpetuating cycle of airway infections and inflammation [3, 4]. Among the pathogens infecting the airways in pwCF, viruses contribute substantially to the deterioration of respiratory function [5].

Given the serious respiratory complications caused by viral infections, pwCF are expected to have higher risk of severe COVID-19. As such, the impact of SARS-CoV-2 infections on pwCF have been closely monitored worldwide via national and international consortia [6-12]. In France, a prospective observational study involving all 47 CF centers has been ongoing since March 2020, with the primary objective of describing the clinical expression of COVID-19 in French pwCF and identifying factors associated with severe outcomes.

Previous studies have revealed that post-lung transplant pwCF are at an increased risk of developing severe COVID-19 [6-11]. However, severity status has been largely examined using healthcare utilization data. Some of the few studies conducted thus far have defined patients with severe COVID-19 based on hospitalization data only. However, indications for hospitalization may differ among countries due to differences across healthcare systems. Moreover, clinical experience suggests that hospitalization practices have evolved since the beginning of the pandemic due to evolving knowledge regarding the management of COVID-19. In the present study, our goal was to present data on all French pwCF diagnosed with

COVID-19 using criteria associated with disease severity rather than with only healthcare utilization. These criteria included hospitalization in intensive care unit (ICU), respiratory support, severe complications (respiratory as well as non-respiratory) or death.

Materials and Methods

Since the first wave of COVID-19 in France in March 2020, all 47 CF centers (which follow over 95% of the 7,500 French pwCF) have been collaborating in conducting a prospective observational study (MR004-2218155) to describe the clinical manifestations of SARS-CoV-2 infection in French pwCF [2]. The study was approved by the Institutional Review Board of the French Society for Respiratory Medicine (*Société de Pneumologie de Langue Française*, #CEPRO_2020-013). All patients received information about the study. In accordance with French laws for observational studies, the requirement for written informed consent was waived.

Data for pwCF infected by SARS-CoV-2 were collected in a dedicated CF-COVID registry nested within the French CF registry [2]. Criteria for positive COVID-19 cases include: (i) positive SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) tests conducted via nasopharyngeal swabs, (ii) typical aspects of COVID-19 seen on thoracic high-resolution computed tomography (HRCT); and/or (iii) serology positive for anti-N SARS-CoV-2 antibodies. Typical HRCT aspects include ground-glass opacities (GGO), consolidation, a bilateral and peripheral distribution of lesions, and a round aspect of lesions [13, 14].

COVID-19 transmission history, clinical, biological, and radiological information, as well as information on medical evolution were prospectively collected and recorded by the caring physicians in the dedicated CF-COVID registry nested within the French CF registry as previously described [6]. The baseline clinical characteristics of SARS-CoV-2 infected pwCF were compared to those of pwCF not diagnosed with SARS-CoV-2 using 2019 data from the

French CF registry [2]. Data from pwCF who developed severe COVID-19 were compared to those with a non-severe infection according to their transplantation status (i.e., non-transplanted vs. post-lung transplant pwCF). COVID-19 cases were classified as severe given at least one of the following criteria: hospitalization in ICU, respiratory support (additional oxygen therapy, high-flow nasal cannula oxygen therapy, non-invasive ventilation [BiPAP (bilevel positive airway pressure), CPAP (continuous positive airway pressure)], invasive ventilation, extracorporeal membrane oxygenation [ECMO]), respiratory complications (acute respiratory distress syndrome [ARDS], a decline in the percent of predicted forced expiratory volume in one second [$ppFEV_1$] >20 in absolute value, large or massive hemoptysis, pneumothorax), severe other complications (myocarditis, encephalopathy, renal failure, sepsis, multi-organ dysfunction failure), or death.

Continuous data were expressed as medians and range values, while categorical data were expressed as numbers and proportions (%). Descriptive statistics were presented for all the study variables. We used Fisher's exact test to compare categorical and qualitative data and implemented Mann Whitney's non-parametric test to evaluate continuous variables. A P-value of less than 5% was interpreted as evidence of a statistically significant difference. The analyses were carried out using SAS 9.4 software (Cary, NC, USA).

Results

Incidence

Between March 1, 2020, and April 30, 2021, 223 pwCF were diagnosed as infected by SARS-CoV-2: 186 had positive SARS-CoV-2 RT-PCR tests conducted via nasopharyngeal swabs; two had negative RT-PCR findings but imaging patterns typical of COVID-19 on computed tomography (CT) scans; and 35 had positive SARS-CoV-2 serology. Among pwCF with positive serology, 13 were asymptomatic and were diagnosed by a systematic

assessment of SARS-CoV-2 serology, whereas 22 had symptomatic infections that were not diagnosed using PCR or CT at the time of infection.

Among the 223 cases, 34 (15%) were considered severe. The majority of the severe cases occurred in adults (≥18 years, n=29, 85.3%) and in post-transplant individuals (n=21, 61.8%). **Figure 1A** shows the evolution in the number of cases per month according to age (adults, ≥18 years vs. children, ≤17 years), transplant status, and nationwide lockdowns (described in **Supplementary Data**).

The testing policy for SARS-CoV-2 in France varied across the first year of the COVID-19 outbreak (detailed in **Supplementary Data**). Access to PCR tests was very limited at the beginning of the epidemic and widely expanded as the epidemic progressed. While variations in testing strategies might explain the variation in the total number of diagnosed cases, severe cases among pwCF would have been diagnosed at any time, explaining the lower variation in the number of severe cases across the first year of the COVID-19 pandemic (**Figure 1B**).

COVID-19 cases as compared with the overall French CF population

We compared the baseline clinical characteristics of 223 SARS-CoV-2 infected pwCF to those of French pwCF not diagnosed with SARS-CoV-2 using data from the French CF Registry [2]. As shown in **Table 1,** COVID-19 CF cases were older than the overall CF population and were more frequently post-transplant individuals (all $p<0.001$). Compared to children, adults with CF were at higher risk at being diagnosed with SARS-CoV-2 infection (odds ratio [OR] = 2.52, 95% confidence interval [CI] = 1.82-3.48, $p <0.001$). The risk of diagnosed SARS-CoV-2 infection was also higher in the post-transplant individuals than in the non-transplanted individuals: 61 were diagnosed among the 853 post-transplant patients (7.1%) as compared to 162 cases diagnosed among the 6,071 non-transplanted patients (2.6%) (OR = 2.68, 95% CI = 1.98-3.63, $p <0.001$).

We found differences in patient characteristics consistent with older age and transplant status, including lower lung function, a more frequent occurrence of CF-associated diabetes, and of the use of treatments such as oral corticosteroids, azithromycin, CF transmembrane conductance regulator (CFTR) modulators (more widely available to adolescents and adults than children <12 years), and long-term oxygen therapy.

Non-transplanted vs. post-transplant cases at infection onset

A comparison of the clinical characteristics of non-transplant *vs.* post-transplant COVID-19 cases at the onset of infection is presented in **Table 2**. The median age of post-transplant pwCF was eight years older than that of non-transplant patients ($p<0.0001$). Post-transplant pwCF had more frequent CF-associated diabetes and systemic arterial hypertension ($p<0.0001$), and were more likely to be treated with oral steroids ($p<0.0001$) and azithromycin ($p=0.04$).

Clinical symptoms at COVID-19 onset are described in **Figure 2**. Among the 223 cases, 56 (25.1%) remained asymptomatic: 44 diagnosed by positive SARS-CoV-2 RT-PCR performed for various reasons (e.g., investigation around a case, systematic testing before traveling), and 13 diagnosed by a systematic assessment of SARS-CoV-2 serology. The remaining 167 cases displayed symptoms quite similar to those described in the general population, which included fever (n=104, 46.6%), fatigue (n=98, 44%), and cough (n=84, 37.6%). Except for severe respiratory symptoms such as dyspnea, respiratory distress, and decreased $ppFEV_1>20$ (observed mainly in post-transplant pwCF), there were no differences in symptoms at infection onset between post-transplant and non-transplanted pwCF.

Non-transplanted vs. post-lung transplant cases

The evolution and treatments of the evaluated cases are described **in Table 3**. Sixty (26.9%) patients were hospitalized, including 31 of the 61 post-transplant pwCF. Post-transplant individuals were more frequently hospitalized than the non-transplanted patients: 31 of the 61

post-transplant patients (50.8%) vs. 29 out of the 162 non-transplanted patients (17.9%) (OR = 4.74, 95% CI = 2.49-9.02, p <0.001).

In 34 cases (15.2%), COVID-19 was considered severe, thus indicating that 28/60 (46.7%) hospitalizations occurred in patients without criteria for severe SARS-CoV-2 infection. Post-transplant pwCF were more at risk to develop a severe form of COVID-19 than non-transplant patients (i.e., 21 of 61 post-transplant patients [34.4%] and 13 of 162 non-transplanted patients [8.0%]; OR = 6.02, 95% CI = 2.77-13.06, p <0.001).

The post-transplant cases not only had more frequent hospitalizations, but also more hospitalizations in the ICU, a longer duration of hospitalization, and a more frequent need for respiratory support, additional IV antibiotics, and systemic corticosteroids (**Table 3**). Only post-transplant pwCF developed acute respiratory distress syndrome on follow-up (ARDS; n=5).

While most cases recovered without short-term sequelae (n=204, 91.5%), 16 (13%) were followed for possible sequelae. Three pwCFs died during the COVID-19 evolution; all were post-lung transplant females. These women were aged 34, 45, and 48 years, had their lung transplant between 2017 and 2018, and were under immunosuppressive drugs (e.g., oral corticosteroids); two had CF-associated diabetes and liver disease. All three patients had relatively preserved lung function, with a $ppFEV_1$>60. They were hospitalized in ICU for a median of 27 days (19-72 days) prior to death. They all required high-flow nasal cannula oxygen therapy and one required invasive ventilation. Two patients developed ARDS, and the third had massive hemoptysis. All received additional systemic corticosteroids.

Risk factors for COVID-19 severity

The baseline clinical characteristics of the pwCF who developed severe COVID-19 were compared to those of the non-severe group to examine risk factors associated with severity (**Table 4**). Among the non-transplanted pwCFs, patients with severe SARS-CoV-2 infection

had the lowest lung function (median ppFEV$_1$ = 54.6% for pwCF with severe infection, 75.1% for pwCF without severe infection, OR=1.04, 95% CI=1.01-1.08) and had more frequent CF-associated diabetes (46.2% of pwCF with severe infection had diabetes as compared to 20.8% of pwCF without severe infection, OR=3.26, 95% CI=1.02-10.4). No differences were observed in the baseline clinical characteristics of post-transplant pwCF according to severity. Long-term azithromycin prior to SARS-CoV-2 infection was not associated with severity status.

Discussion

In this national multicenter study, we describe the clinical expression of COVID-19 in French pwCF during the first year of the pandemic. Given the serious respiratory complications caused by viral infections in CF, pwCF are expected to be at a higher risk of COVID-19 as well as at a higher risk of disease severity [5]. However, the number of diagnosed COVID-19 cases in pwCF is rather low, though the risk is increased in adults *vs.* children similarly to the general population [15, 16]. By originally using objective criteria for defining COVID-19 severity, we showed that risk factors included low lung function and diabetes in non-transplanted pwCF. Post-transplant pwCF were more likely to develop severe COVID-19 in congruence with their immunosuppression status, their older age and their more frequent comorbidities such as diabetes and systemic arterial hypertension.

In this study, the severity of COVID-19 acute care was examined based on markers of clinical severity rather than relying solely on hospitalization rates as a proxy for severity, as reported by other researchers [6-11]. Hence, COVID-19 was classified as severe when the patient was hospitalized in ICU, needed respiratory support, developed severe complications, or died. This might explain why the number of hospitalized pwCF was double that of those

who developed severe COVID-19. Especially at the beginning of the pandemic, some pwCF were hospitalized for fear of the impact of infection on CF disease without markers of clinical severity. Thus, by applying the classification described herein, we demonstrated that the main independent risk factor for severe COVID-19 was lower lung function at the onset of infection in non-transplanted pwCF, as well as post-transplant status. Of note, lung function was not associated with severe COVID-19 in post-transplant patients.

The present results confirm our preliminary report within data obtained during the first wave of the COVID-19 pandemic as well as in international studies [6-11] showing that SARS-CoV-2 infections occur infrequently in pwCF (with a cumulative incidence of 3% as of April 2021). A recent systematic review showed that the risk of developing a SARS-CoV-2 infection was not increased in pwCF as compared to the general population, with 339 cases reported among 1,236 pwCF from the European CF Society Patient Registry [17]. Two hypotheses have been proposed to explain these findings: the routine use of hand washing, mask wearing, and physical distancing to prevent human-to-human infection, as well as the younger age of the overall cohort of pwCF as compared to the general population [18].

We observed that children with CF were less likely to be diagnosed with SARS-CoV-2 as compared to adults, a finding comparable to the general population [19]. Only 10% of children with CF and COVID-19 developed severe infections, according to a previous international study conducted during the first wave of the pandemic that showed that children had mostly mild disease presentations [20]. Several hypotheses have been proposed to explain the lower incidence of COVID-19 in children. Innate and adaptive responses to SARS-CoV-2 have been suggested as possible protective factors against SARS-CoV-2 infection [16]. In contrast to adults, children have higher susceptibility to various respiratory viruses, higher rates of closely spaced immunization, and therefore a greater likelihood of stimulated trained immunity. This may provide cross-protection against other viruses through

memory cells [21, 22]. Children might also seem less likely to be infected because of their higher rates of asymptomatic disease.

Our study confirms that severe cases of COVID-19 occur relatively infrequently in pwCF. These data are in marked contrast with previous reports of other respiratory viral infections. For example, the H1N1-influenza pandemic in 2009 led to a statistically significant decline in lung function and decreased survival in pwCF [23]. Moreover, RSV and rhinovirus infections are strongly associated with pulmonary exacerbations in pwCF [24, 25]. Several studies have shown that bacterial airway infections (i.e., *Pseudomonas aeruginosa*) are often preceded by viral infections [26]. It was observed *in vitro* that exposure of CF airway epithelial cells to *Pseudomonas aeruginosa* enhanced SARS-CoV-2 infectivity [27]. Long-term studies are necessary to fully appreciate the impact of COVID-19 on lung function decline in patients with pwCF.

Compared to non-transplanted patients, post-transplant pwCF were more frequently diagnosed as infected and more likely to develop severe COVID-19. In congruence with their immunosuppression status, the post-transplant pwCF were also older and had more comorbidities (e.g., CF-associated diabetes and systemic arterial hypertension). Therefore, these patients required greater utilization of healthcare resources, including more frequent hospitalizations, ICU admissions, a higher necessity for respiratory support, and additional antibiotics and systemic corticosteroids. Only post-transplant individuals developed SARS-CoV-2-associated ARDS or died. These results agree with those of previous international and national reports [6-11]. Additionally, this severity status might mirror the severe COVID-19 evolution described in non-CF immunocompromised patients [28-30].

Azithromycin is often prescribed to pwCF as it reduces pulmonary exacerbations and induces modest improvements in lung function [31]. Hence, one-third of pwCF from the French Registry are treated with low-dose long-term azithromycin. Despite the absence of

randomized clinical trials supporting its prescription, short courses of azithromycin have been widely used in COVID-19 management in the general population due to their immunomodulatory and antiviral properties [32-34]. We observed that pwCF infected by SARS-CoV-2 were more frequently under azithromycin at the onset of infection than the remaining cohort of French pwCF (51.6% of the cases). This may reflect the older age of these cases (vs. causal etiologies). Nevertheless, these findings contradict the assumption that this treatment might prevent infection. Moreover, this result is consistent with a cross-sectional study conducted in Spain in patients treated with long-term macrolides for chronic respiratory disease [35]. Indeed, we found no differences in COVID-19 severity between pwCF never treated with azithromycin and those who received this treatment at some point during the course of their infection.

This prospective study was conducted through the French CF reference network, thus covering all pediatric and adult CF centers and all transplant centers. Additional study strengths are that the standardized study questionnaire was distributed at the start of the pandemic outbreak and that the study was nested within the French CF Registry. The main limitation of this work is that mild cases may have remained undiagnosed due to the absence of sufficient testing for COVID-19. This limitation might not alter our conclusions, as our main results concerned severe cases that would be unlikely to be missed. Another limitation is small number of severe cases of COVID-19, due to their infrequent occurrence, which compelled us to make only univariate associations without possibility of adjustment for confounding factors.

Conclusions

After one year of the COVID-19 pandemic, we found that the cumulative incidence of COVID-19 remained low in pwCF, probably thanks to the fact that pwCF are acclimated to masks, hand hygiene, and social distancing to limit exposure and avoid infection. Non-

transplanted pwCF appear to have better COVID-19 outcomes than anticipated (i.e., as compared to other respiratory viral infections). However, compared to non-transplanted patients, post-transplant pwCF patients were more frequently diagnosed as infected and more likely to develop severe COVID-19. This study highlights the need to pursue preventative strategies, including SARS-CoV-2 vaccinations for pwCF as well as for the general population to protect susceptible patients and decrease viral spread. Finally, as the pandemic is still unresolved and new SARS-CoV-2 variants are arising that may result in differential expression of COVID-19, close monitoring of CF cohorts is necessary to fully understand the consequences of COVID-19 in pwCF.

NOTES

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Tables

Table 1. **COVID-19 cases in people with cystic fibrosis (pwCF) as compared with the overall French CF population**

	pwCF diagnosed with SARS-CoV-2 infection n = 223	**Remaining pwCF from the French CF registry [2] n = 6924**	**P-value**
Male, n (%)	110 (49.3)	3618 (52.3)	0.39
Age (years), median (range: min-max)	29.3 (0-69)	21.6 (0.6-85.1)	**<0.0001**
Children (<18 years-old), n (%)	48 (21.5)	2832 (40.9)	**<0.0001**
Exocrine pancreatic insufficiency, n (%)	196 (87.9)	5555 (80.2)	**0.023**
Post-transplant, n (%)	61 (27.4)	853 (12.3)	**<0.0001**
***CFTR* mutations**			
F508del homozygotes, %	95 (42.6)	2831 (40.9)	0.22
F508del heterozygotes, %	100 (44.8)	2919 (42.2)	
Other	28 (12.6)	1174 (17)	
Lung function, $ppFEV_1$[(1)]			
median (range: min-max)	77.6 (22.3-129.6)	83.9 (15.2- 164.4)	**<0.0001**
<40%, n (%)	23 (10.3)	420 (6.1)	**0.01**
[40-70%[, n (%)	64 (28.7)	1417 (20.5)	
>=70%, n (%)	126 (56.5)	3997 (57.7)	
Nutritional status, BMI Z-score[(2)]			
median (range: min-max)	-0.3 (-2.7-4.6)	-0.3 (-7.5-14.11)	0.57
Comorbidities			
ABPA, n (%)	29 (13)	588 (8.5)	**0.01**
CF liver disease, n (%)	45 (20.2)	1107 (16)	0.09
CF related diabetes, n (%)	77 (34.5)	1401 (20.2)	**<0.0001**
Treatments prior SARS-Cov-2 infection			
Inhaled corticosteroids, n (%)	121 (54.3)	3612 (52.2)	0.54
Oral corticosteroids (> 3 months), n (%)	54 (24.2)	890 (12.9)	**<0.0001**
Azithromycin, n (%)	115 (51.6)	2458 (35.5)	**<0.0001**
CFTR Modulators, n (%)	68[(3)] (30.5)	1591 (23)	**0,009**
Long-term oxygen therapy (> 3 months), n (%)	20 (9)	305 (4.4)	**0.001**
Long-term non-invasive ventilation (> 3 months), n (%)	16 (7.2)	314 (4.5)	0.06

[(1)]Knudson equations [36]; [(2)]Rolland-Cachera equations [37]; [(3)]12 ivacaftor; 42 lumacaftor-ivacaftor; 22 elexacaftor-tezacaftor-ivacaftor (8 patients had 2 CFTR modulators).

Abbreviations: pwCF, people with cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; $ppFEV_1$, percent predicted forced expiratory volume in 1 s; BMI, body mass index; ABPA, allergic bronchopulmonary aspergillosis.

Table 2. **Non-transplanted vs. post-transplant people with cystic fibrosis (pwCF) at SARS-CoV-2 infection onset**

	Non-transplanted n = 162	**Post-transplant n = 61**	**P-value**
Male, n (%)	81 (50)	29 (47.5)	0.77
Age (years), median (range: min-max)	26.0 (0-69)	34.1 (13-63)	**<0.0001**
Exocrine pancreatic insufficiency, n (%)	137 (84.6)	59 (96.7)	**0.01**
***CFTR* mutations**			0.71
F508del homozygotes, n (%)	66 (40.7)	29 (47.5)	
F508del heterozygotes, n (%)	75 (46.3)	25 (41)	
Other	21 (13)	7 (11.5)	
Influenza vaccine in the past 12 months, n (%)	92 (56.8)	26 (42.6)	0.07
$ppFEV_1$[(1)], median (range: min-max)	72.2 (22.3-129.6)	83.7 (24.3-113.8)	0.07
BMI Z-score[(2)], median (range: min-max)	-0.1 (-2-4.6)	-0.6 (-2.7-1.9)	**0.0004**
Chronic infection by *Pseudomonas aeruginosa* in past 12 months, n (%)	76 (46.9)	16 (26.2)	**<0.0001**
Comorbidities			
ABPA, n (%)	24 (14.8)	5 (8.2)	0.1
CF liver disease, n (%)	33 (20.4)	12 (19.7)	0.86
CF related diabetes, n (%)	37 (22.8)	40 (65.6)	**<0.0001**
Systemic arterial hypertension, n (%)	5 (3.1)	23 (37.7)	**<0.0001**
Treatments prior SARS-Cov-2 infection			
Inhaled corticosteroids, n (%)	94 (58)	18 (29.5)	**<0.0001**
Oral corticosteroids, n (%)	8 (4.9)	43 (70.5)	**<0.0001**
CFTR Modulators[(3)], n (%)	68 (42)	0	**NA**[(3)]
Azithromycin, n (%)	65 (40.1)	36 (59)	**0.04**

[(1)]Knudson equations [36]; [(2)]Rolland-Cachera equations [37]; [(3)]NA: not appropriate as CFTR modulators are not indicated in post-transplant patients.

Abbreviations: pwCF, people with cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; $ppFEV_1$, percent predicted forced expiratory volume in 1 s; BMI, body mass index; ABPA, allergic bronchopulmonary aspergillosis.

Table 3. COVID-19 severity and outcomes of non-transplanted vs. post-transplant people with cystic fibrosis (pwCF)

	All pwCF n = 223	Non-transplanted n = 162	Post-transplant n = 61	Non-transplanted vs post-transplant P-value
Patients' management				**<0.0001**
Ambulatory care, n (%)	163 (73.1)	133 (82.1)	30 (49.2)	
Hospitalization, n (%)	60 (26.9)	29 (17.9)	31 (50.8)	
Hospitalization setting				**<0.0001**
Medical ward (non-ICU), n (%)	46 (20.6)	27 (16.7)	19 (31.1)	
ICU, n (%)	14 (6.3)	2 (1.2)	12 (19.7)	
Hospitalization duration (days), median (range)	10.5 (1-72)	6 (1-40)	15 (3-72)	**<0.0001**
Patient discharge, n (%)				**<0.0001**
<10 days, n (%)	26 (11.7)	18 (11.1)	8 (13.1)	
10–19 days, n (%)	22 (9.9)	9 (5.6)	13 (21.3)	
20–29 days, n (%)	7 (3.1)	0	7 (11.5)	
>30 days, n (%)	5 (2.2)	1 (0.6)	4 (6.6)	
Respiratory support				
Additional oxygen therapy, n (%)	23 (10.3)	7 (4.3)	16 (26.2)	**<0.0001**
Non-invasive ventilation (BIPAP, CPAP), n (%)	1 (0.4)	1 (0.6)	0	--
High flow nasal canula oxygen therapy, n (%)	8 (3.6)	2 (1.2)	6 (9.8)	**<0.0001**
Invasive Ventilation, n (%)	2 (0.9)	0	2 (3.3)	0.07
ECMO	0	0	0	--
Additional treatments				
Additional IV antibiotics, n (%)	36 (16.1)	18 (11.1)	18 (29.5)	**<0.0001**
Additional oral antibiotics, n (%)	63 (28.3)	51 (31.5)	12 (19.7)	0.09
Additional Azithromycin, n (%)	8 (3.6)	6 (3.7)	2 (3.3)	1
Additional systemic corticosteroids, n (%)	28 (12.6)	6 (3.7)	22 (36.1)	**<0.0001**
Hydroxychloroquine, n (%)	2 (0.9)	0	2 (3.3)	0.07

Sarilumab, n (%)	4 (1.8)	0	4 (6.6)	**<0.0001**
Respiratory complications	40 (17.9)	27 (16.7)	13 (21.3)	0.44
Respiratory exacerbation, n (%)	32 (14.3)	25 (15.4)	7 (11.5)	0.53
Bacterial pneumonia, n (%)	8 (3.6)	3 (1.9)	5 (8.2)	**0.037**
ARDS, n (%)	5 (2.2)	0	5 (8.2)	**<0.0001**
Hemoptysis, n (%)	3 (1.3)	1 (0.6)	2 (3.3)	0.18
Overall evolution				
Recovered without short-term sequelae, n (%)	204 (91.5)	149 (92)	55 (90.2)	0.79
Unknown / possible sequelae to follow, n (%)	16 (13)			
Died, n (%)	3 (1.3)	0	3 (4.9)	**0.02**

Abbreviations: ARDS, acute respiratory distress syndrome ; BIPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; ECMO, extracorporeal membrane oxygenation; IV, intravenous

1 ***Table 4.*** **Risk factors for COVID-19 severity in non-transplanted and post-transplant people with cystic fibrosis (pwCF)**

	Non-transplanted pwCF			Post-transplant pwCF		
	Severe	**Non severe**	**OR [95% CI]**	**Severe**	**Non severe**	**OR [95% CI]**
Number of pwCF, n (%)	**13 (8)**	**149 (92)**		**21 (35)**	**40 (65)**	
Clinical characteristics						
Male, n (%)	5 (38.5)	76 (51.0)	0.6 [0.19-1.92]	8 (38.1)	21 (52.5)	0.56 [0.19-1.64]
Age (years), median (range: min-max)	29.7 (0.6-44.3)	25.9 (0-69)	1.01 [0.96-1.05]	34.1 (12.5-48.1)	32.8 (16.6-63.4)	0.99 [0.94-1.04]
Exocrine pancreatic insufficiency, n (%)	12 (92.3)	125 (83.9)	2.3 [0.29-18.53]	19 (90.5)	40 (100)	NA
F508del homozygotes, n (%)	4 (30.8)	62 (41.6)	0.62 [0.18-2.1]	8 (38.1)	21 (52.5)	0.56 [0.19-1.64]
ppFEV1[(1)], median (range: min-max)	54.6 (23.3-71.8)	75.1 (22.3-129.6)	**1.04 [1.01-1.08]**	90 (27.2-113.8)	82.2 (24.3-106.3)	1 [0.97-1.02]
BMI Z-score[(2)], median (range: min-max)	-0.3 (-1.4-3.9)	-0.1 (-2-4.6)	0.87 [0.52-1.46]	-0.5 (-2.3-0.4)	-0.6 (-2.7-1.9)	1.02 [0.56-1.84]
Comorbidities						
ABPA, n (%)	2 (15.4)	22 (14.8)	1.04 [0.22-4.92]	2 (9.5)	3 (7.5)	1.3 [0.2-8.46]
CF liver disease, n (%)	4 (30.8)	29 (19.5)	1.84 [0.53-6.39]	4 (19)	8 (20.0)	0.94 [0.25-3.58]
CF related diabetes, n (%)	6 (46.2)	31 (20.8)	**3.26 [1.02-10.4]**	13 (61.9)	27 (67.5)	0.78 [0.26-2.35]
Treatments prior SARS-CoV-2 infection						
Inhaled corticosteroids, n (%)	9 (69.2)	94 (63.1)	1.32 [0.39-4.49]	9 (42.9)	9 (22.5)	2.58 [0.83-8.06]
Oral corticosteroids, n (%)	2 (15.4)	9 (6.0)	2.83 [0.54-14.74]	15 (71.4)	28 (70.0)	1.07 [0.33-3.43]

CFTR Modulators, n (%)	4 (30.8)	64 (43.0)	0.59 [0.17-2.0]	0 (0)	0 (0)	NA[3]
Azithromycin, n (%)	6 (46.2)	73 (49.0)	0.89 [0.29-2.77]	14 (66.7)	22 (55.0)	1.64 [0.55-4.93]

[1]Knudson equations [36]; [2]Rolland-Cachera equations [37]; [3]NA: not appropriate as CFTR modulators are not indicated in post-transplant patients.

Abbreviations: pwCF, people with cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; $ppFEV_1$, percent-predicted forced expiratory volume in 1 s; BMI, body mass index; ABPA, allergic bronchopulmonary aspergillosis.

Figure legends

***Figure 1*. Incidence during the first year of the COVID-19 pandemic (March 2020 to April 2021) in adults (non-transplanted and post-transplant) and children with cystic fibrosis (CF).** These figures depicts the evolution in (A) the overall number of cases, and (B) the number of severe cases. The scatter with smooth lines graphs (A) and the histograms (B) were generated using Microsoft Excel®.

***Figure 2*. Distribution of the main symptoms at SARS-CoV-2 infection onset in people with cystic fibrosis (pwCF) according to transplantation status.**

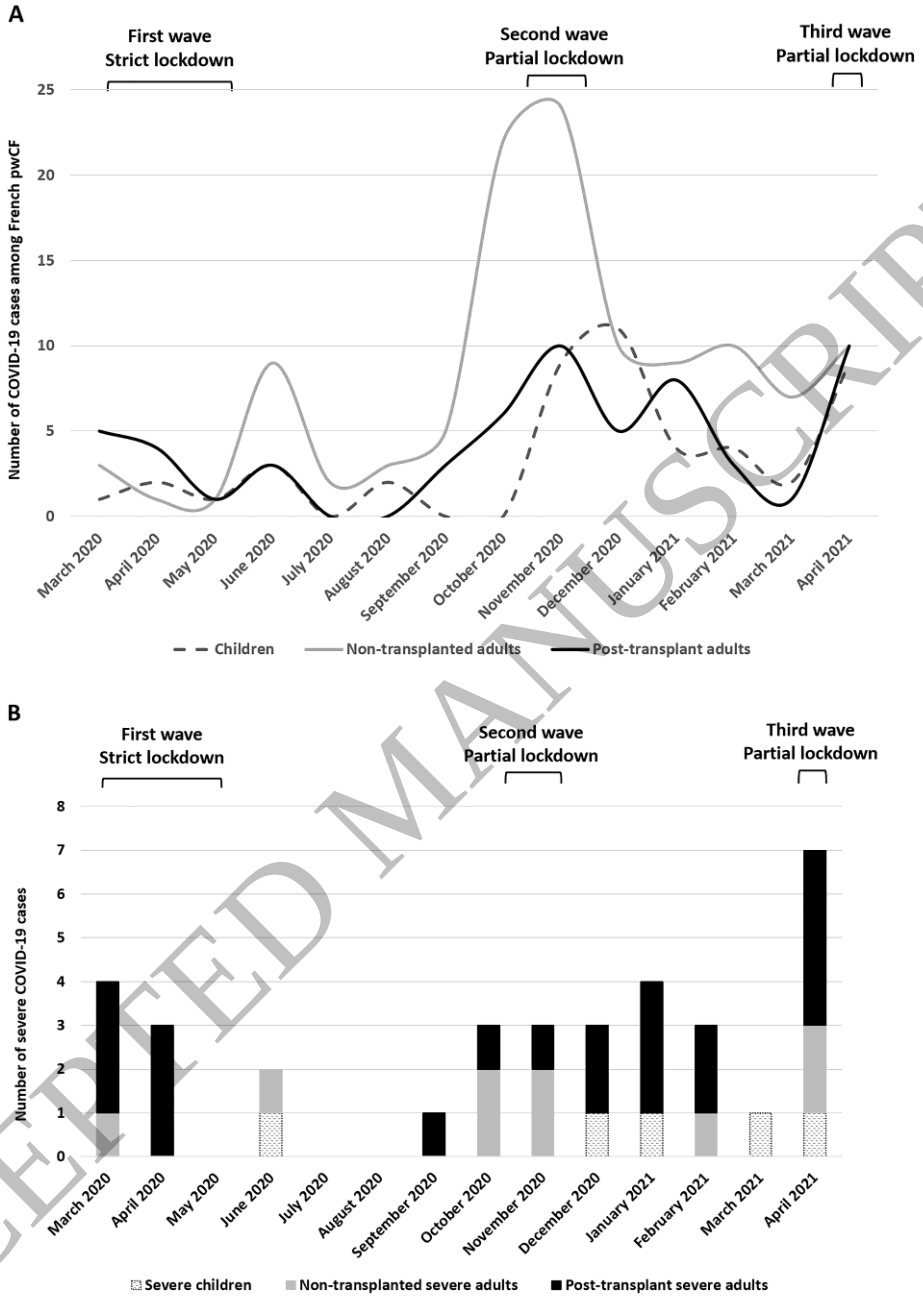

Figure 1
160x226 mm (0.4 x DPI)

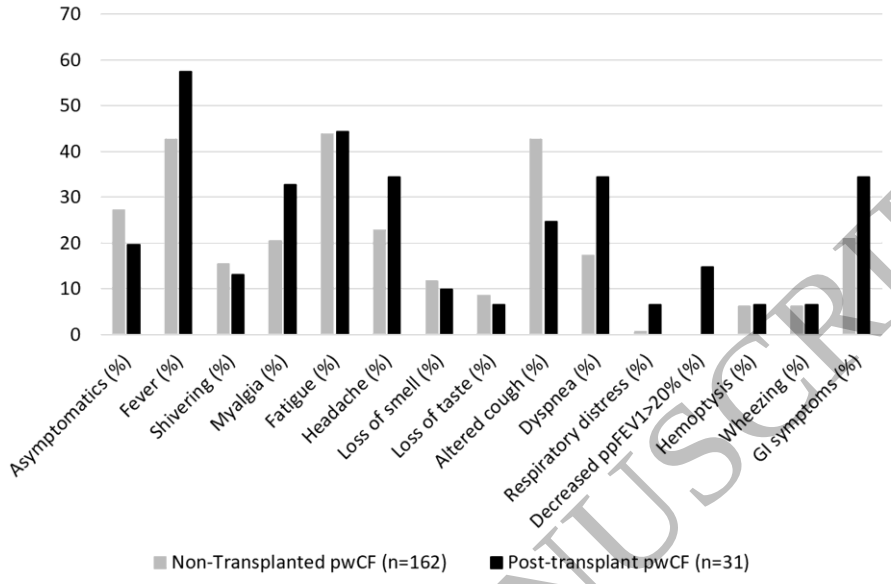

Figure 2
160x226 mm (0.4 x DPI)