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► **To cite this version:**

Harriet Corvol, Sandra de Miranda, Clémence Dehillotte, Lydie Lemonnier, Raphael Chiron, et al.. Cumulative Incidence and Risk Factors for Severe Coronavirus Disease 2019 in French People With Cystic Fibrosis. *Clinical Infectious Diseases*, 2022, 10.1093/cid/ciac333 . hal-03827698

**HAL Id: hal-03827698**

**<https://hal.science/hal-03827698>**

Submitted on 15 Jul 2024

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

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14

1 **Abstract**

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

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

9 **Results:** As of April 30, 2021, 223 pwCF were diagnosed with COVID-19, with higher risks  
10 in adults ( $\geq 18$  years, odds ratio [OR]=2.52, 95% confidence interval [CI]=1.82-3.48) and  
11 post-transplant individuals (OR=2.68, 95% CI=1.98-3.63). Sixty (26.9%) patients were  
12 hospitalized, with an increased risk in post-transplant individuals (OR=4.74, 95% CI=2.49-  
13 9.02). In 34 (15%) cases, COVID-19 was considered severe; 28/60 (46.7%) hospitalizations  
14 occurred in patients without objective criteria of severity. Severe cases occurred mostly in  
15 adults (85.3%) and post-transplant pwCF (61.8%, OR=6.02, 95% CI=2.77-13.06). In non-  
16 transplanted pwCF, risk factors for severity included low lung function (median ppFEV<sub>1</sub>  
17 54.6% vs. 75.1%, OR=1.04, 95% CI=1.01-1.08) and CF-associated diabetes (OR=3.26, 95%  
18 CI=1.02-10.4). While most cases recovered without sequelae (n=204, 91.5%), 16 (13%) were  
19 followed for possible sequelae, and three post-transplant females died.

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

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

25

## 1 **Introduction**

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

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

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

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

#### 4 **Materials and Methods**

5 Since the first wave of COVID-19 in France in March 2020, all 47 CF centers (which follow  
6 over 95% of the 7,500 French pwCF) have been collaborating in conducting a prospective  
7 observational study (MR004-2218155) to describe the clinical manifestations of SARS-CoV-  
8 2 infection in French pwCF [2]. The study was approved by the Institutional Review Board of  
9 the French Society for Respiratory Medicine (*Société de Pneumologie de Langue Française*,  
10 #CEPRO\_2020-013). All patients received information about the study. In accordance with  
11 French laws for observational studies, the requirement for written informed consent was  
12 waived.

13 Data for pwCF infected by SARS-CoV-2 were collected in a dedicated CF-COVID registry  
14 nested within the French CF registry [2]. Criteria for positive COVID-19 cases include: (i)  
15 positive SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) tests  
16 conducted via nasopharyngeal swabs, (ii) typical aspects of COVID-19 seen on thoracic high-  
17 resolution computed tomography (HRCT); and/or (iii) serology positive for anti-N SARS-  
18 CoV-2 antibodies. Typical HRCT aspects include ground-glass opacities (GGO),  
19 consolidation, a bilateral and peripheral distribution of lesions, and a round aspect of lesions  
20 [13, 14].

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

1 French CF registry [2]. Data from pwCF who developed severe COVID-19 were compared to  
2 those with a non-severe infection according to their transplantation status (i.e., non-  
3 transplanted vs. post-lung transplant pwCF). COVID-19 cases were classified as severe given  
4 at least one of the following criteria: hospitalization in ICU, respiratory support (additional  
5 oxygen therapy, high-flow nasal cannula oxygen therapy, non-invasive ventilation [BiPAP  
6 (bilevel positive airway pressure), CPAP (continuous positive airway pressure)], invasive  
7 ventilation, extracorporeal membrane oxygenation [ECMO]), respiratory complications  
8 (acute respiratory distress syndrome [ARDS], a decline in the percent of predicted forced  
9 expiratory volume in one second [ppFEV<sub>1</sub>] >20 in absolute value, large or massive  
10 hemoptysis, pneumothorax), severe other complications (myocarditis, encephalopathy, renal  
11 failure, sepsis, multi-organ dysfunction failure), or death.

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

## 18

## 19 **Results**

### 20 *Incidence*

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

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

3 Among the 223 cases, 34 (15%) were considered severe. The majority of the severe cases  
4 occurred in adults ( $\geq 18$  years,  $n=29$ , 85.3%) and in post-transplant individuals ( $n=21$ , 61.8%).

5 **Figure 1A** shows the evolution in the number of cases per month according to age (adults,  
6  $\geq 18$  years vs. children,  $\leq 17$  years), transplant status, and nationwide lockdowns (described in  
7 **Supplementary Data**).

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

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

15 We compared the baseline clinical characteristics of 223 SARS-CoV-2 infected pwCF to  
16 those of French pwCF not diagnosed with SARS-CoV-2 using data from the French CF  
17 Registry [2]. As shown in **Table 1**, COVID-19 CF cases were older than the overall CF  
18 population and were more frequently post-transplant individuals (all  $p < 0.001$ ). Compared to  
19 children, adults with CF were at higher risk at being diagnosed with SARS-CoV-2 infection  
20 (odds ratio [OR] = 2.52, 95% confidence interval [CI] = 1.82-3.48,  $p < 0.001$ ). The risk of  
21 diagnosed SARS-CoV-2 infection was also higher in the post-transplant individuals than in  
22 the non-transplanted individuals: 61 were diagnosed among the 853 post-transplant patients  
23 (7.1%) as compared to 162 cases diagnosed among the 6,071 non-transplanted patients  
24 (2.6%) (OR = 2.68, 95% CI = 1.98-3.63,  $p < 0.001$ ).



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

#### 6 *Non-transplanted vs. post-transplant cases at infection onset*

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

13 Clinical symptoms at COVID-19 onset are described in **Figure 2**. Among the 223 cases, 56  
14 (25.1%) remained asymptomatic: 44 diagnosed by positive SARS-CoV-2 RT-PCR performed  
15 for various reasons (e.g., investigation around a case, systematic testing before traveling), and  
16 13 diagnosed by a systematic assessment of SARS-CoV-2 serology. The remaining 167 cases  
17 displayed symptoms quite similar to those described in the general population, which  
18 included fever ( $n=104$ , 46.6%), fatigue ( $n=98$ , 44%), and cough ( $n=84$ , 37.6%). Except for  
19 severe respiratory symptoms such as dyspnea, respiratory distress, and decreased  $ppFEV_{1>20}$   
20 (observed mainly in post-transplant pwCF), there were no differences in symptoms at  
21 infection onset between post-transplant and non-transplanted pwCF.

#### 22 *Non-transplanted vs. post-lung transplant cases*

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

1 post-transplant patients (50.8%) vs. 29 out of the 162 non-transplanted patients (17.9%) (OR  
2 = 4.74, 95% CI = 2.49-9.02,  $p < 0.001$ ).

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

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

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

#### 22 ***Risk factors for COVID-19 severity***

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

1 had the lowest lung function (median ppFEV<sub>1</sub> = 54.6% for pwCF with severe infection,  
2 75.1% for pwCF without severe infection, OR=1.04, 95% CI=1.01-1.08) and had more  
3 frequent CF-associated diabetes (46.2% of pwCF with severe infection had diabetes as  
4 compared to 20.8% of pwCF without severe infection, OR=3.26, 95% CI=1.02-10.4). No  
5 differences were observed in the baseline clinical characteristics of post-transplant pwCF  
6 according to severity. Long-term azithromycin prior to SARS-CoV-2 infection was not  
7 associated with severity status.

8

## 9 **Discussion**

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

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

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

7 The present results confirm our preliminary report within data obtained during the first wave  
8 of the COVID-19 pandemic as well as in international studies [6-11] showing that SARS-  
9 CoV-2 infections occur infrequently in pwCF (with a cumulative incidence of 3% as of April  
10 2021). A recent systematic review showed that the risk of developing a SARS-CoV-2  
11 infection was not increased in pwCF as compared to the general population, with 339 cases  
12 reported among 1,236 pwCF from the European CF Society Patient Registry [17]. Two  
13 hypotheses have been proposed to explain these findings: the routine use of hand washing,  
14 mask wearing, and physical distancing to prevent human-to-human infection, as well as the  
15 younger age of the overall cohort of pwCF as compared to the general population [18].

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

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

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

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

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

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

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

## 22 **Conclusions**

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

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

10

## 11 **NOTES**

12 **Author Contributions:** Conceptualization and methodology, H.C, C.L, L.L, A.K, and  
13 P.R.B.; data provision: all authors; data interpretation, H. C., C. L., L. L., A. K., and P.R.B.;  
14 writing—review and editing, H.C and P.R.B. All authors have read and agreed to the  
15 published version of the manuscript.

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23 Françoise TROUSSIER, CHU D'ANGERS; Laurence WEISS, HOPITAUX  
24 UNIVERSITAIRES DE STRASBOURG; Nathalie WIZLA, CHU DE LILLE.



1 **Funding:** This work was supported by the Association Vaincre La Mucoviscidose and Filière  
2 de Santé Maladies rares Muco-CFTR. These funders had no role in the conduct or reporting  
3 of this study.

4 **Conflicts of Interest:** CM reports consulting fees from Vertex unrelated to this work;  
5 payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or  
6 educational events for the Viartis symposia 2021 and Zambon symposia 2021; support for  
7 attending meetings and/or travel from Zambon for ECFS 2019 and JFM (French CF  
8 meeting); participation on a Data Safety Monitoring Board or Advisory Board for Vertex  
9 (institutional fees) and Zambon (personal fees); and an unpaid position as the Head of the  
10 French CF society. PRB reports grants or contracts unrelated to this work and paid to the  
11 author's institution from GSK and Vertex; consulting fees from Astra-Zeneca, Chiesi, GSK,  
12 Inmed, and Vertex; personal fees for lectures from Astra-Zeneca, Boehringer Ingelheim,  
13 Chiesi, GSK, Novartis,  
14 Pfizer, Vertex, Viartis, and Zambon; and support for attending meetings and/or travel from  
15 Astra-Zeneca, Zambon, and Viartis. The authors have no other actual or potential conflicts of  
16 interest to declare.

17

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## 1 Tables

### 2 *Table 1. COVID-19 cases in people with cystic fibrosis (pwCF) as compared with the* 3 *overall French CF population*

	<b>pwCF diagnosed with SARS-CoV-2 infection n = 223</b>	<b>Remaining pwCF from the French CF registry [2] n = 6924</b>	<b>P-value</b>
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)	<b>&lt;0.0001</b>
Children (<18 years-old), n (%)	48 (21.5)	2832 (40.9)	<b>&lt;0.0001</b>
Exocrine pancreatic insufficiency, n (%)	196 (87.9)	5555 (80.2)	<b>0.023</b>
Post-transplant, n (%)	61 (27.4)	853 (12.3)	<b>&lt;0.0001</b>
<b>CFTR mutations</b>			
F508del homozygotes, %	95 (42.6)	2831 (40.9)	0.22
F508del heterozygotes, %	100 (44.8)	2919 (42.2)	
Other	28 (12.6)	1174 (17)	
<b>Lung function, ppFEV<sub>1</sub><sup>(1)</sup></b>			
median (range: min-max)	77.6 (22.3-129.6)	83.9 (15.2- 164.4)	<b>&lt;0.0001</b>
<40%, n (%)	23 (10.3)	420 (6.1)	<b>0.01</b>
[40-70%], n (%)	64 (28.7)	1417 (20.5)	
>=70%, n (%)	126 (56.5)	3997 (57.7)	
<b>Nutritional status, BMI Z-score<sup>(2)</sup></b>			
median (range: min-max)	-0.3 (-2.7-4.6)	-0.3 (-7.5-14.11)	0.57
<b>Comorbidities</b>			
ABPA, n (%)	29 (13)	588 (8.5)	<b>0.01</b>
CF liver disease, n (%)	45 (20.2)	1107 (16)	0.09
CF related diabetes, n (%)	77 (34.5)	1401 (20.2)	<b>&lt;0.0001</b>
<b>Treatments prior SARS-Cov-2 infection</b>			
Inhaled corticosteroids, n (%)	121 (54.3)	3612 (52.2)	0.54
Oral corticosteroids (> 3 months), n (%)	54 (24.2)	890 (12.9)	<b>&lt;0.0001</b>
Azithromycin, n (%)	115 (51.6)	2458 (35.5)	<b>&lt;0.0001</b>
CFTR Modulators, n (%)	68 <sup>(3)</sup> (30.5)	1591 (23)	<b>0.009</b>
Long-term oxygen therapy (> 3 months), n (%)	20 (9)	305 (4.4)	<b>0.001</b>
Long-term non-invasive ventilation (> 3 months), n (%)	16 (7.2)	314 (4.5)	0.06

4 <sup>(1)</sup>Knudson equations [36]; <sup>(2)</sup>Rolland-Cachera equations [37]; <sup>(3)</sup>12 ivacaftor; 42 lumacaftor-ivacaftor;  
 5 22 elexacaftor-tezacaftor-ivacaftor (8 patients had 2 CFTR modulators).

6 *Abbreviations:* pwCF, people with cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance  
 7 regulator; ppFEV<sub>1</sub>, percent predicted forced expiratory volume in 1 s; BMI, body mass index; ABPA,  
 8 allergic bronchopulmonary aspergillosis.

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

	<b>Non-transplanted</b>	<b>Post-transplant</b>	<b>P-value</b>
	<b>n = 162</b>	<b>n = 61</b>	
Male, n (%)	81 (50)	29 (47.5)	0.77
Age (years), median (range: min-max)	26.0 (0-69)	34.1 (13-63)	<b>&lt;0.0001</b>
Exocrine pancreatic insufficiency, n (%)	137 (84.6)	59 (96.7)	<b>0.01</b>
<b>CFTR mutations</b>			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 <sub>1</sub> <sup>(1)</sup> , median (range: min-max)	72.2 (22.3-129.6)	83.7 (24.3-113.8)	0.07
BMI Z-score <sup>(2)</sup> , median (range: min-max)	-0.1 (-2-4.6)	-0.6 (-2.7-1.9)	<b>0.0004</b>
Chronic infection by <i>Pseudomonas aeruginosa</i> in past 12 months, n (%)	76 (46.9)	16 (26.2)	<b>&lt;0.0001</b>
<b>Comorbidities</b>			
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)	<b>&lt;0.0001</b>
Systemic arterial hypertension, n (%)	5 (3.1)	23 (37.7)	<b>&lt;0.0001</b>
<b>Treatments prior SARS-Cov-2 infection</b>			
Inhaled corticosteroids, n (%)	94 (58)	18 (29.5)	<b>&lt;0.0001</b>
Oral corticosteroids, n (%)	8 (4.9)	43 (70.5)	<b>&lt;0.0001</b>
CFTR Modulators <sup>(3)</sup> , n (%)	68 (42)	0	<b>NA<sup>(3)</sup></b>
Azithromycin, n (%)	65 (40.1)	36 (59)	<b>0.04</b>

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

6 **Abbreviations:** pwCF, people with cystic fibrosis; CFTR, cystic fibrosis transmembrane  
 7 conductance regulator; ppFEV<sub>1</sub>, percent predicted forced expiratory volume in 1 s; BMI,  
 8 body mass index; ABPA, allergic bronchopulmonary aspergillosis.

9

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

	All pwCF n = 223	Non- transplanted n = 162	Post- transplant n = 61	Non-transplanted vs post-transplant P-value
<b>Patients' management</b>				<b>&lt;0.0001</b>
Ambulatory care, n (%)	163 (73.1)	133 (82.1)	30 (49.2)	
Hospitalization, n (%)	60 (26.9)	29 (17.9)	31 (50.8)	
<b>Hospitalization setting</b>				<b>&lt;0.0001</b>
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)	
<b>Hospitalization duration</b> (days), median (range)	10.5 (1-72)	6 (1-40)	15 (3-72)	<b>&lt;0.0001</b>
Patient discharge, n (%)				<b>&lt;0.0001</b>
<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)	
<b>Respiratory support</b>				
Additional oxygen therapy, n (%)	23 (10.3)	7 (4.3)	16 (26.2)	<b>&lt;0.0001</b>
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)	<b>&lt;0.0001</b>
Invasive Ventilation, n (%)	2 (0.9)	0	2 (3.3)	0.07
ECMO	0	0	0	--
<b>Additional treatments</b>				
Additional IV antibiotics, n (%)	36 (16.1)	18 (11.1)	18 (29.5)	<b>&lt;0.0001</b>
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)	<b>&lt;0.0001</b>
Hydroxychloroquine, n (%)	2 (0.9)	0	2 (3.3)	0.07



Sarilumab, n (%)	4 (1.8)	0	4 (6.6)	<b>&lt;0.0001</b>
<b>Respiratory complications</b>	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)	<b>0.037</b>
ARDS, n (%)	5 (2.2)	0	5 (8.2)	<b>&lt;0.0001</b>
Hemoptysis, n (%)	3 (1.3)	1 (0.6)	2 (3.3)	0.18
<b>Overall evolution</b>				
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)	<b>0.02</b>

1

2 *Abbreviations:* ARDS, acute respiratory distress syndrome ; BIPAP, bilevel positive airway

3 pressure; CPAP, continuous positive airway pressure; ECMO, extracorporeal membrane

4 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]
<b>Number of pwCF, n (%)</b>	<b>13 (8)</b>	<b>149 (92)</b>		<b>21 (35)</b>	<b>40 (65)</b>	
<b>Clinical characteristics</b>						
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 <sup>(1)</sup> , median (range: min-max)	54.6 (23.3-71.8)	75.1 (22.3-129.6)	<b>1.04 [1.01-1.08]</b>	90 (27.2-113.8)	82.2 (24.3-106.3)	1 [0.97-1.02]
BMI Z-score <sup>(2)</sup> , 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]
<b>Comorbidities</b>						
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)	<b>3.26 [1.02-10.4]</b>	13 (61.9)	27 (67.5)	0.78 [0.26-2.35]
<b>Treatments prior SARS-CoV-2 infection</b>						
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 <sup>(3)</sup>
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

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

3 *Abbreviations:* pwCF, people with cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; ppFEV<sub>1</sub>, percent-predicted forced expiratory

4 volume in 1 s; BMI, body mass index; ABPA, allergic bronchopulmonary aspergillosis.

1 **Figure legends**

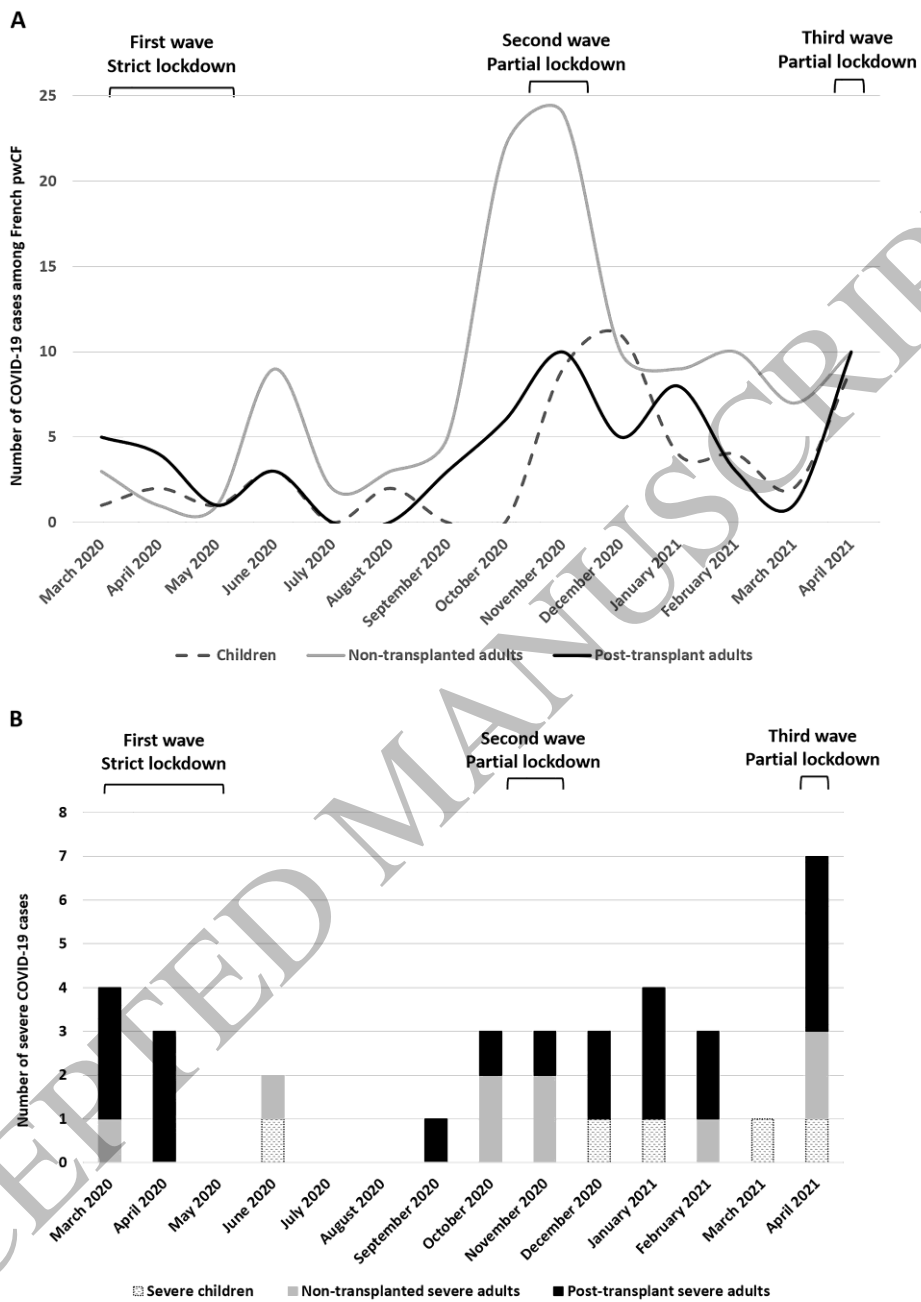
2 ***Figure 1. Incidence during the first year of the COVID-19 pandemic (March 2020 to***  
3 ***April 2021) in adults (non-transplanted and post-transplant) and children with cystic***  
4 ***fibrosis (CF).*** These figures depicts the evolution in (A) the overall number of cases, and (B)  
5 the number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

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

9

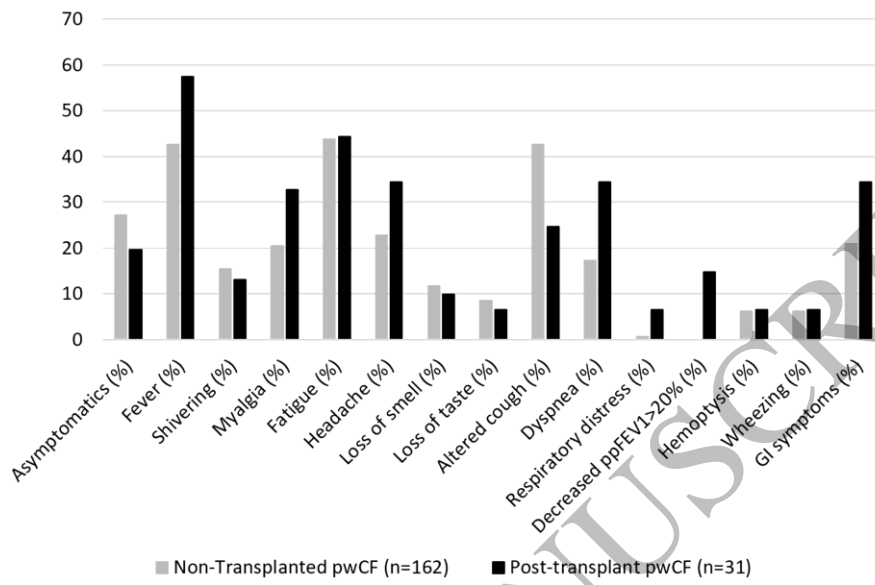
10

ACCEPTED MANUSCRIPT



1  
2  
3  
4

Figure 1  
160x226 mm (0.4 x DPI)



1  
2  
3

Figure 2  
160x226 mm (0.4 x DPI)