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SARS-CoV-2 infection in children with cystic fibrosis: A cross-sectional multicenter study in Spain. New waves, new knowledge

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Abstract

Introduction: The association between viral infections and pulmonary exacerbations in children with cystic fibrosis (cwCF) is well established. However, the question of whether cwCF are at a higher risk of COVID-19 or its adverse consequences remains controversial.

Methods: We conducted an observational, multicenter, cross-sectional study of cwCF infected by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)

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between March 2020 and June 2022, (first to sixth COVID-19 pandemic waves) in Spain. The study aimed to describe patients' basal characteristics, SARS-CoV-2 clinical manifestations and outcomes, and whether there were differences across the pandemic waves.

Results: During study time, 351 SARS-CoV2 infections were reported among 341 cwCF. Median age was 8.5 years (range 0–17) and 51% were female. Cases were unevenly distributed across the pandemic, with most cases (82%) clustered between November 2021 and June 2022 (sixth wave, also known as Omicron Wave due to the higher prevalence of this strain in that period in Spain). Most cwCF were asymptomatic (24.8%) or presented with mild Covid-19 symptoms (72.9%). Among symptomatic, most prevalent symptoms were fever (62%) and increased cough (53%). Infection occurring along the sixth wave was the only independent risk factor for being symptomatic. Just eight cwCF needed hospital admission. No multisystem inflammatory syndrome, persisting symptoms, long-term sequelae, or deaths were reported.

Conclusions: Spanish current data indicate that cwCF do not experience higher risks of SARS-CoV-2 infection nor worse health outcomes or sequelae. Changes in patients' basal characteristics, clinical courses, and outcomes were detected across waves. While the pandemic continues, a worldwide monitoring of COVID-19 in pediatric CF patients is needed.

KEYWORDS

COVID-19, pandemic, pediatrics, vaccination

1 | INTRODUCTION

SARS-CoV-2 (severe acute respiratory syndrome by coronavirus-2) has caused catastrophic effects worldwide creating the biggest health crisis in the century.[1] Since declared a global pandemic in March 2020, it has caused over 6 million deaths and has overwhelmed most healthcare systems.[2] The fatality rate and severity of the coronavirus disease 2019 (COVID-19) is highly affected by age, ethnic group or underlying medical conditions[3] cystic fibrosis (CF), a progressive genetic disorder that affects the lungs, pancreas, and other organs is one of the most common chronic lung diseases in children and young adults.[4] In this context, initial expectations regarding COVID-19 outcomes and mortality rates for patients with CF have been surpassed,[5] as reported experiences, in different countries, have shown better outcomes than anticipated[6–14] In CF patients, viral respiratory tract infections are usually more severe than in the general population, with an increased risk of complications, an associated decrease in lung function and a higher mortality.[15] However, CF patients have not exhibited higher rates of SARS-CoV-2 infection compared to the general population, with no apparent impact on the severity of their CF.[10,12,14,16–18] As reported by McClenaghan et al.,[19] from the Cystic Fibrosis Registry Global Harmonization Group, CF patients have similar outcomes to the general population when infected with SARS-CoV-2. Different previous studies among Europe have revealed similar findings, with worse outcomes associated with older age, CF-related diabetes, and organ transplantation.[10,12,14,17,20,21]

In children, SARS-CoV-2 infection is generally less severe than in adults, but specific information on COVID-19 in children with cystic fibrosis (cwCF) is still scarce and inconsistent. A large study conducted by the CF Registry analyzed 105 cases of COVID-19 in cwCF, revealing that most children were managed in the community (71%), that cwCF requiring hospitalization had lower lung function and reduced body mass index (BMI) compared to their peers, and that only one pediatric death, which was not directly attributed to COVID-19, was reported. Interestingly, unlike adults, pediatric patients with solid organ transplants did not seem to experience worse outcomes.[22] On the other hand, some studies did find worst outcomes with a higher risk of hospitalization from SARS-CoV-2 in cwCF,[21,22] but these findings need to be treated with caution because of the small number of severe cases reported. Finally, new variants, such as Omicron have shown partial vaccine escape and higher transmissibility generating massive outbreaks with decreased severity and mortality rates,[23] but there is limited specific data on how these new variants might affect cwCF.

This report aims to provide an overview of the demographic and previous CF-related clinical characteristics, the symptoms, and the

outcomes among laboratory-confirmed COVID-19 cases in cwCF in Spain.

2 | METHODS

We present an observational, cross-sectional, multicenter study, including 26 Spanish Pediatric CF units. Inclusion criteria were cwCF with confirmed SARS-CoV-2 infection diagnosed by reverse transcription polymerase chain reaction (RT-PCR) or rapid antigen test between 7 March 2020 and 7 June 2022. CF units encouraged CF patients to perform diagnostic tests (RT-PCR or rapid antigen test) if they had new symptoms or close contact with a person diagnosed with COVID-19. All confirmed positive cases in CF patients younger than 18 were included, regardless of the presence of symptoms.

A web-based structured questionnaire was created and the same data were assessed in all centers, collecting information on sex, age, ethnicity, CFTR genetic mutation, latest ppFEV$_1$ (percent predicted forced expiratory volume in 1 s, using Global Lung initiative data as reference), BMI, pancreatic status, having at least one *Pseudomonas aeruginosa* isolation in respiratory secretions in the year before the infection, CF-related diabetes, arterial hypertension, organ transplant, and SARS-CoV-2 vaccination status. We also calculated age- and sex-specific z-score of the BMI for children over 2 years old and nutritional status was defined using sex and age-specific cut-off points of the BMI based on the International Obesity Task Force (IOTF) standards of reference[24] As outcomes, we evaluated the clinical manifestations of SARS-CoV-2 infection, the need to add any treatments or respiratory support, the recurrence, the hospitalization or intensive care unit (ICU) admissions and the mortality. The distribution of cases throughout the pandemic and the differences between the six waves included in the study period were also evaluated. A comparison analysis between hospitalized and nonhospitalized children was not performed due to the low number of admissions in this pediatric cohort. By contrast, we evaluated if there were any risk factors for symptomatic infection by SARS-CoV-2.

Descriptive and statistical inference tools were used to analyze categorical and numerical variables, Student's *t*-test, χ^2 or Fisher's exact test were used to determine differences across pandemic waves. Median and interquartile rank or median and standard deviation were calculated for quantitative variables according to normality and percentages were calculated for qualitative variables. A multivariate analysis was performed to evaluate the possible risk factors for suffering from a symptomatic infection by SARS-CoV-2, considering the variable "any symptom" as dependent, and sex, age, pandemic wave, pancreatic insufficiency, latest ppFEV$_1$, *P. aeruginosa* in last year and vaccination status as independent variables. For all analyses, the bilateral significance level was set at $p < .05$.

For this study, the data were collected and validated within the framework of the European Cystic Fibrosis Society Patient Registry (www.ecfs.eu/ecfspr) and approved by the Research Ethics Committee of the participating hospitals in Spain. Only data from people with CF who provided written consent, including consent to use their data for future research, is used. This enabled the framework for collecting data regarding SARS-CoV-2 infection.

For those participants not included in the ECFSPR, specific informed consent was obtained. Registration was carried out according to Spanish Laws 14/2007 on Biomedical Research and 15/1999 on the Protection of Personal Data. The study received no funding source.

3 | RESULTS

During the study period (March 2020–June 2022, first six pandemic waves in Spain), 351 SARS-CoV2 infections were reported among 341 cwCF. Ten recurrent infections were reported.

3.1 | Participants' demographic and clinical characteristics

Demographic and previous CF-related clinical characteristics of the cwCF cohort are provided in Table 1. Median participant's age was 8.5 years (range 0–17 years) and 51% were female. According to IOTF, 14.2% were underweight, 75.5% healthy weight, 7.5% overweight, and 2.7% were obese. None suffered from arterial hypertension. Regarding transplants, none of the cwCF had undergone a solid organ transplantation but two children were on a lung transplant-list and one had received a bone marrow transplantation due to sickle cell disease.

If we assume that our total cohort of cwCF under 18 years-old in Spain is 1115 (according to the ECFSPR Annual Report 2020[25]), and there are no missing data, we could estimate an approximate incidence of SARS-CoV-2 infection of 36.67% in the first 27 pandemic months.

3.2 | Timeline of SARS-CoV-2 infections over the pandemic

Infections occurred in an uneven way throughout the pandemic. While a few cases were reported during the first 20 months of pandemic (March 2020–November 2021), a significant higher number of infections clustered during the 2021–2022 Northern Hemisphere winter, with 63% of infections being reported between December 2021 and February 2022. Indeed, up to 109 cases (31%) came about in a single month (February 2022). According to the different COVID-19 pandemic waves stablished by the Spanish Health Department, the sixth wave counted with the highest number of reported cases by far since 82% of infections in cwCF occurred between November 2021 and June 2022. Cases distribution by month and pandemic wave are summarized in Figure 1.

TABLE 1 Demographic and previous CF-related clinical characteristics of cwCF infected with SARS-CoV-2.

	n (% or ± SD)
Sex (*N* = 352)	
Male	173 (49.15%)
Female	179 (50.85%)
Age at infection (*N* = 352)	
Median age (range); years	8.5 (0–17)
Mean age (years)	8.96 (±5.18)
0–1 (infants)	29 (8.24%)
2–5 (preschoolers)	75 (21.31%)
6–11 (children)	119 (33.81%)
12–17 (adolescents)	129 (36.64%)
CFTR genotype (*N* = 327)	
Homozygous F508del	98 (29.97%)
Heterozygous F508del	163 (49.85%)
Other	66 (20.18%)
BMI (*N* = 324)	
Mean BMI	17.35 (±3.51)
Pancreatic status (*N* = 327)	
Pancreatic insufficiency	241 (73.7%)
Pancreatic sufficiency	86 (26.3%)
Lung function (*N* = 227)	
Mean ppFEV1	93.04 (±17.79)
>90%	144 (63.44%)
71%–90%	57 (25.11%)
40%–70%	25 (11.01%)
<40%	1 (0.44%)
CF-related diabetes (*N* = 327)	8 (2.45%)
Pseudomonas aeruginosa[a] (*N* = 327)	91 (27.83%)
Solid organ transplantation (*N* = 351)	0 (0%)
Listed for organ transplant (*N* = 351)	2 (0.57%)
CFTR modulator therapy (*N* = 327)	
On CFTR modulator therapy	106 (32.41%)
Ivacaftor	2 (0.61%)
Lumacaftor/Ivacaftor	30 (9.17%)
Tezacaftor/Ivacaftor	33 (10.09%)
Elexacaftor/Tezacaftor/Ivacaftor	41 (12.54%)

Note: ppFEV1 in the previous year (children ≥5 years old). Continuous variables are described as means ± SD and categorical variables as *n* and percentage (%).

Abbreviations: BMI, body mass index; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; cwCF, children with cystic fibrosis; *n*, number of subjects; ppFEV1, best percent predicted forced expiratory volume in 1 s; SARS-CoV-2, severe acute respiratory syndrome by coronavirus-2; SD, standard deviation.

[a]*Pseudomonas aeruginosa* (at least one isolated in the previous 12 months).

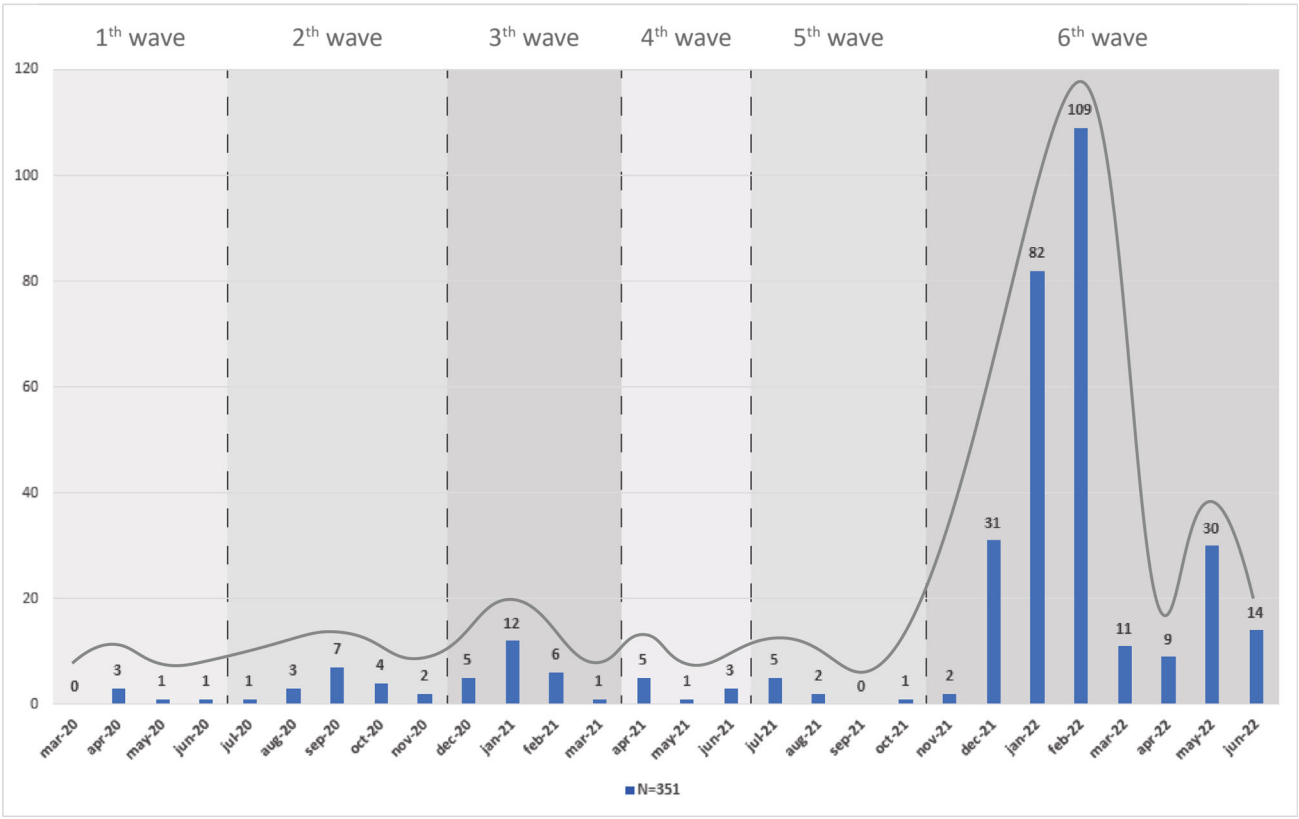

FIGURE 1 Monthly distribution of SARS-CoV-2 infections over the COVID-19 pandemic among Spanish children with cystic fibrosis. Pandemic waves stablished by the Spanish Health Department: first wave March–June 2020; second wave July–November 2020; third wave December 2020–March 2021; fourth wave April–June 2021; fifth wave July–October 2021; sixth wave November 2021–June 2022.

3.3 | Diagnosis, clinical manifestations, hospitalization, treatment, vaccination status against SARS-CoV-2, and recurrences

Data related to the diagnosis methods, symptomatology, level of care, treatment, vaccination status and infection recurrence are shown in Table 2. Thirty-seven percent of the cwCF were diagnosed by positive respiratory sample PCR, while 63% were diagnosed after a positive rapid antigen test. Almost a quarter of the cwCF had an asymptomatic course of the disease. Among those with symptoms, the most prevalent symptom was fever (62%), with 54%, 32%, 13%, and 37% having, respectively, at least one respiratory, gastrointestinal, ENT (ear, nose, throat), and general symptom. The overall specific prevalence of every symptom, and comparatively during the first five waves and during the sixth one is shown in Figure 2 and Supporting Information: Table 1. Beyond this, none of the children developed MIS-C.

The majority of cases were managed at home (97.72%), with only 2.28% requiring hospital admission (eight children whose characteristics are detailed in Supporting Information: Table 2). One child was admitted to ICU due to a severe dehydration secondary to salt loss syndrome during 2020 summer. There were no children admitted to ICU because of respiratory problems. Similarly, up to 87% of cwCF with SARS-CoV-2 infection did not require any specific treatment apart from common antipyretic, analgesic or nonsteroid anti-inflammatory drugs. Some children were treated with oral antibiotics (12.5%), intravenous antibiotics (2%), or systemic steroids (1%).

Regarding SARS-CoV-2 vaccination status, 72,5% of children 5 years old and older had received at least one dose of the vaccine before the infection.

Finally, 10 cases of infection recurrence were reported during the study period. At the time of the writing of this paper (March 2023), all cwCF included in this study were fully recovered from the SARS-CoV-2 infection. No persisting symptoms, long-term sequelae or deaths were reported.

3.4 | Differences between the sixth SARS-CoV-2 wave and the previous five waves

The analysis comparing the sixth SARS-CoV-2 wave with the previous five waves is shown in Table 3. No differences related to sex and age were found, however, cwCF infected during the first five waves had worse basal lung function than those diagnosed along the sixth wave (mean ppFEV$_1$ 86.2% vs. 94.5%; $p = .008$)

TABLE 2 SARS-CoV-2 diagnosis, clinical manifestations, vaccination status, and recurrence among Spanish CF children infected between March 2020 and June 2022.

	n (%)
Method of diagnosis (*n* = 351)	
Positive respiratory sample PCR	129 (36.75)
Positive rapid antigen testing	222 (63.25)
Symptoms (*n* = 351)[a]	
Asymptomatic	87 (24.79)
Any symptoms	264 (75.21)
MIS-C	0 (0)
Level of care (*n* = 351)	
Home self-care	342 (97.72)
Hospital admission	8 (2.28)
Intensive care unit admission	1 (0.28)
Additional or new pharmacological treatment and respiratory support (*n* = 351)	
Any additional or new treatment or support	47 (13.39)
Additional or new oral antibiotics	44 (12.54)
Additional or new intravenous antibiotics	7 (1.99)
Additional or new systemic steroids	4 (1.14)
Additional or new oxygen therapy	0 (0)
Additional or new noninvasive mechanical ventilation	0 (0)
Additional or new invasive mechanical ventilation	0 (0)
Doses of vaccination against SARS-CoV-2[b] (*n* = 266)	
None before the infection	73 (27.44)
At least one dose before the infection (1–3 doses)	193 (72.56)
Recurrence of infection (*n* = 341)	10 (2.93)

Abbreviations: CF, cystic fibrosis; MIS-C, pediatric multisystem inflammatory syndrome related with COVID-19; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome by coronavirus-2.

[a]The proportion of each symptom was calculated from the symptomatic cases and not from the overall sample (*n* = 264).

[b]Children <5 years old excluded (vaccine not indicated).

During the first five waves, the majority of children were diagnosed by PCR test (56/63; 88.9%). By contrast, cwCF were mainly diagnosed by antigen test over the sixth wave (215/288; 74.6%).

Regarding the manifestations associated with the infection, there were more symptomatic cases along the sixth wave as compared with the previous five ones (77.4% vs. 65.1%; $p = .04$). Indeed, the fact of getting the infection during the sixth wave was the only risk factor for being symptomatic, both in the univariate and the multivariate analysis (independently of the rest of variables included; odds ratio 2.41 [95% confidence interval 1.14–5.1], $p = .021$). In addition, we refer to Figure 2 to see the statistical differences between both periods of time in regard with every specific symptom.

Rate of hospitalization and burden of treatment was significantly higher along the first five waves. While six of the cwCF were hospitalized between the pandemic outbreak and November 2021, only two required hospital admission from then to June 2022 ($p < .01$). Moreover, a higher percentage of cwCF received both intravenous (7.94% vs. 0.69%; $p = .003$) and oral antibiotics (22.2% vs. 10.42%; $p = .01$) during the first studied period as compared to the second one.

Most children five years old and older who underwent SARS-CoV-2 infection during the sixth wave had been vaccinated (84.7%) as compared with those who got infected during the previous waves (11.36%, $p < .001$).

4 | DISCUSSION

In this national multicenter study, we describe the clinical expression of SARS-CoV-2 infection in cwCF alongside the sixth national waves established by the Spanish Health Department. To our knowledge, this is the largest published case series of SARS-CoV-2 infection in cwCF, with 341 unique patients (351 total episodes). The vast majority had a mild disease, no need of treatment and all of them fully recovered.

Most hospitalizations were related to CF symptoms (dehydration, allergic bronchopulmonary aspergillosis) or concurrent issues (bone marrow transplant), and just one due to pulmonary exacerbation. One child was admitted to ICU due to a severe dehydration and none needed oxygen or mechanical ventilation, so ICU admission appears to be exceptional.

However, after the onset of the pandemic, there was a significant reduction in CF pulmonary exacerbations requiring hospitalizations. Some studies suggest that general infection control measures such as masking, social distancing, lockdowns, and school closures, might have contributed to this substantial reduction in non-COVID respiratory infections and hospital admissions seen not only in patients with CF but also in the general population.[17,18] Therefore, our hospitalization results have to be contextualized in this scenario.

When comparing our admission rates with other studies that investigated the incidence of SARS-CoV-2 infection in cwCF, we found that our cohort had a significantly lower rate of hospitalization. However, there is a limitation associated with a small number of hospitalizations in our study that may impact the generalization and reliability of these findings. Bain et al. published the results of the CF Registry Global Harmonization Group collecting data from 13 countries from February to August 2020. It showed that 22.9% of 105 children infected were admitted to hospital versus 2.28% in our study.[22] Both cohorts have similar baseline clinical characteristics, good pulmonary function test and few CF-associated comorbidities. Colombo et al. reported a hospitalization rate of 16% (13 of 81 cwCF) and death rate of 2.46% (two of 81 cwCF) among all CF patients since March 2020 to June 2021.[12] We speculate that the substantial

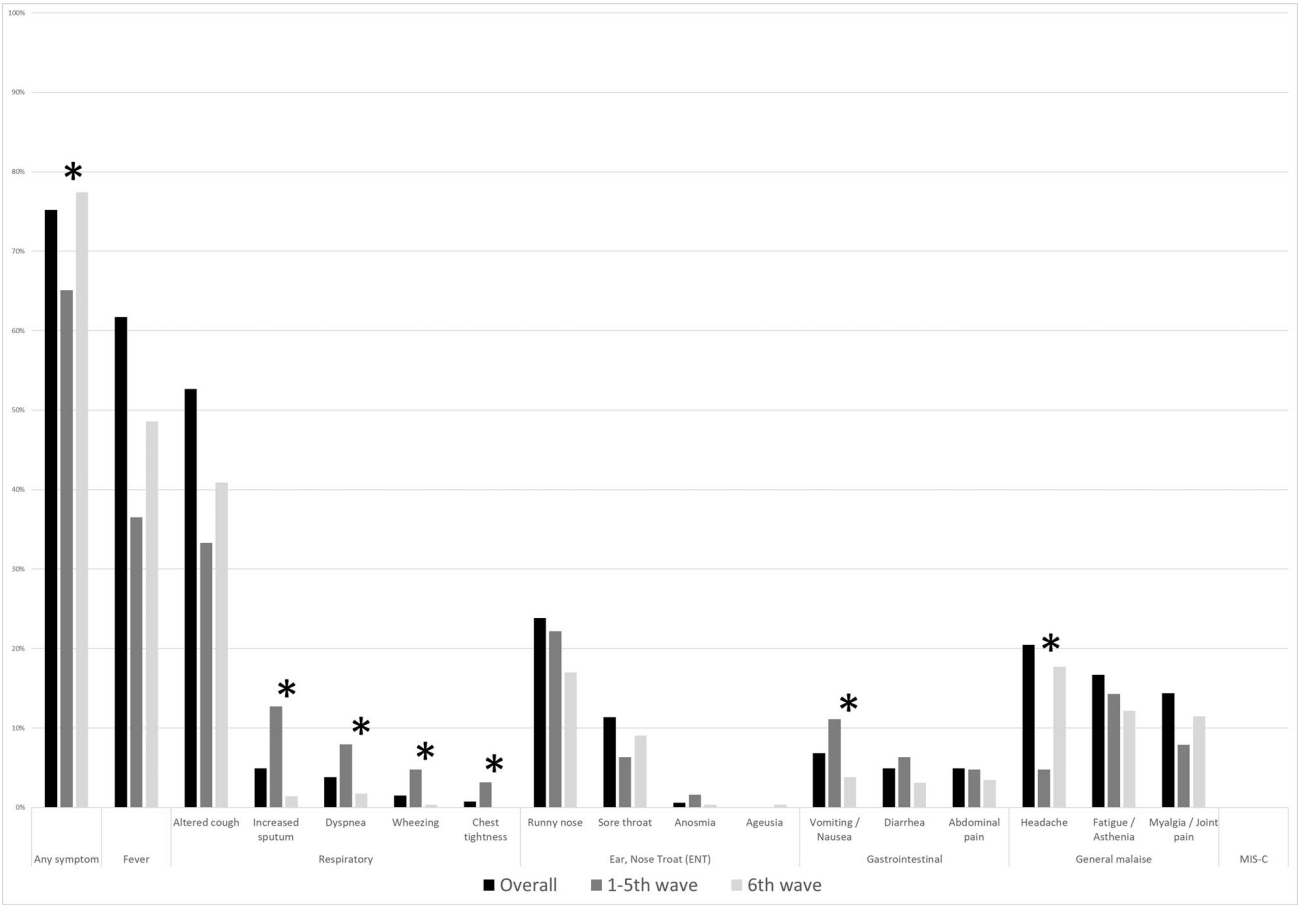

FIGURE 2 Distribution of symptoms according to overall cases, 1–5th wave and 6th wave among Spanish CF children infected between March 2020 and June 2022. Pandemic waves stablished by the Spanish Health Department: first wave March–June 2020; second wave July–November 2020; third wave December 2020–March 2021; fourth wave April–June 2021; fifth wave July–October 2021; sixth wave November 2021–June 2022. *$p < .05$ when comparing the sixth wave with the previous ones.

disparity in hospitalization rates may be attributed to our study's larger sample size, encompassing more pandemic waves that featured SARS-CoV2 variants that are more contagious but cause milder symptoms, as well as the potential protective effect of SARS-CoV2 vaccination. Moreover, the differing admission criteria in the initial months of the pandemic, when patients were primarily admitted for observation and medical monitoring due to the limited understanding of the implications of SARS-CoV-2 infection in individuals with chronic respiratory conditions, may also account for this contrast. Furthermore, the scarcity of diagnostic tests in the early stages of the pandemic and their exclusive use in healthcare centers meant that probably only the most serious cases requiring medical assistance were diagnosed. Our study revealed differences in the utilization of SARS-CoV-2 diagnostic tests between the six waves, with a predominance of rapid antigen testing in the sixth wave, as opposed to PCR sampling in the preceding waves.

Our study found that getting the infection during the sixth wave was the only significant risk factor for being symptomatic, regardless of the other variables. Nevertheless, other studies[5] in CF patients (adults and pediatrics) showed that age >40 years, at least one F508del mutation and pancreatic insufficiency was associated with symptomatic status.

The Omicron variant (B.1.1.529) has led to a change in the SARS-CoV-2 infection pattern in cwCF, when pediatric cases increased dramatically worldwide,[26,27] despite the initial lower incidence. This variant showed to be more contagious but led to milder illness forms of SARS-CoV-2 pediatric infection.[28] Thouvenin et al.[29] studied the impact of the Omicron variant and compared with previous data in cwCF. They found an increase from 9% to 32% in SARS-CoV-2 infections in their cwCF cohort ($n = 76$) during the Omicron wave. Four patients (17%) required hospitalization, two of which needed oxygen supplementation, with no ICU admissions. Our study revealed a marked rise in SARS-CoV2 infections during the Omicron wave, accounting for 82% of all cases, yet with lower hospitalization rates. Furthermore, our Spanish pediatric CF patients diagnosed in the sixth wave exhibited more symptoms than those diagnosed in prior waves, with statistically significant differences noted in headache and vomiting/nausea. However, respiratory symptoms such as increased sputum or dyspnea were more frequent in the first five waves. Patients diagnosed during the first wave had a more severe CF lung disease, which can explain the appearance of more respiratory symptoms compared to those of the sixth wave, who had better

TABLE 3 Differences between the sixth SARS-CoV-2 wave and the previous five waves among Spanish CF children infected between March 2020 and June 2022.

Variable	First five waves $n = 63$	Sixth wave $n = 288$	p Value
Sex (female)	35; 55.6%	144; 50.0%	.42
Median age (years)	7; (4–14)	9; (5–14)	.12
Pancreatic insufficiency	50; 80.6%	191; 72.1%	.16
Positive PCR	56; 88.9%	73; 25.4%	**<.001**
Positive rapid antigen testing	7; 11.1%	215; 74.6%	**<.001**
Lung function ($ppFEV_1$)	86.2%	94.5%	**.008**
Symptomatic	41; 65.1%	223; 77.4%	**.04**
Hospitalization	6; 9.52%	2; 0.69%	**<.01**
Intravenous antibiotics	5; 7.94%	2; 0.69%	**.003**
Oral antibiotics	14; 22.2%	30; 10.42%	**.01**
Systemic steroids	2; 3.17%	2; 0.69%	.15
On CFTR modulator therapy	16; 25.8%	87; 32.8%	.28
SARS-CoV-2 vaccination[a]	5; 11.36%	188; 84.7%	**<.001**

Note: The proportion of each value was calculated from the nonmissing data in each group as depicted by *n*. ppFEV1 in the previous year (children ≥5 years old), according to GLI equations. Continuous variables are described as median and interquartile rank and categorical variables as *n* and percentage.

Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; GLI, global lung function initiative; *n*, number of subjects; PCR, polymerase chain reaction; ppFEV1, best percent predicted forced expiratory volume in 1 s; SARS-CoV-2, severe acute respiratory syndrome by coronavirus-2.

[a]At least one dose of SARS-CoV-2 vaccine. Children <5 years old excluded (vaccine not indicated); $n = 266$.

$ppFEV_1$. This is also important in the rate of hospitalization and the use of antibiotics in our cohort, which were higher in the first five waves compared to the sixth one. We interpret these results because of the differences in severity of CF lung disease in patients diagnosed in the different waves, having a more severe lung disease those diagnosed in first five waves and, consequently, requiring more hospitalizations and antibiotics. However, the finding of a higher rate of hospital admissions in the first five waves ($n = 6$, 9.5%) as compared with the sixth one ($n = 2$, .7%; $p < .01$) should be interpreted with caution due to the limited number of hospitalizations that could lead to a bias. Vaccination could be another reason of milder infections in the sixth wave compared to children diagnosed in first five waves, who had a lower rate of vaccination against SARS-CoV-2 before the infection.

Our data on asymptomatic patients (almost 25%) agree with other studies.[5,22,30,31] These subjects underwent the diagnostic test because they were close contacts or as screening for elective hospital admission during the pandemic, following the recommendations established by Public Health Services.

Our findings indicate that cwCF have a comparable risk of developing severe SARS-CoV-2 infection to those with other chronic respiratory conditions, which is relatively low. The Pediatric Assembly of the European Respiratory Society conducted a survey, which revealed that only a small number of children with chronic respiratory conditions required hospitalization and ventilatory support, mainly those with bronchopulmonary dysplasia.[32]

If we compare our sample with patients diagnosed with a similar disease such as primary ciliary dyskinesia (PCD), an international longitudinal study found that 3.4% of this pediatric population had a SARS-CoV-2 infection with only one patient hospitalized and no ICU admissions (12.5%).[33] The evolution of PCD is similar to CF and it could be expected that the risk of severe SARS-CoV-2 infection in both cases were similar. However, this study only included eight children with PCD compared to our 341 children sample and this can explain the differences in hospitalization rates.

It is remarkable that none of the patients had MIS-C-related symptoms. Several reviews encompassing a multitude of studies indicate the characteristics of patients who developed MIS-C and the presence of comorbidities. These comorbidities are present in 23%–45% of the patients who developed MIS-C.[2,3,8] Among them, the most frequent is obesity, although in a very variable range according to the studies (16.4%–80%), with the presence of a chronic pulmonary disease (mainly asthma) being the second most frequent comorbidity.[2,8] However, the reviews are heterogeneous and some even conclude that there is no comorbidity that is actually associated with a higher risk of MIS-C, which is consistent with the results of our study.[8]

Our study has certain limitations as it was cross-sectional and retrospective, and may, therefore, be subject to missing data due to

the voluntary reporting bias. While our study presents a relatively large cohort of SARS-CoV-2 infection in cwCF in Spain, we recognize the inherent limitations resulting from the restricted sample size. Therefore, we strongly believe that continuous surveillance and comprehensive descriptions of the impact of COVID-19 in individuals with CF are crucial. To overcome this sample-size limitation, future studies could consider conducting multicenter analyses, incorporating data from multiple countries. By publishing each country's experiences, we can foster collaboration within the scientific community and facilitate future meta-analyses, ultimately enhancing our understanding of COVID-19's effects on cwCF.

Hence, we cannot accurately estimate the real incidence of SARS-CoV2 infection in cwCF as we only included reported cases. Since at the time of the study, large-scale antibody testing among the CF population was not in place, the study could not include all infected patients with asymptomatic infection. Therefore, a real and accurate prevalence could not be calculated. Nevertheless, we have attempted to minimize the impact of missing data by involving all pediatric CF units in Spain, which maintain a close monitoring of their patients. Additionally, since the majority of cases were mild, we were unable to identify risk factors linked to a poorer prognosis.

In conclusion, this study describes, to our knowledge, the largest case series of SARS-CoV- 2 infection in cwCF. Our findings in this population suggest that it is generally mild and does not necessitate hospitalization or additional treatment. We can also affirm that in Spain, the vast majority of patients were infected in the sixth wave, when the clinical picture of SARS-CoV-2 infection was different with more symptoms such as headache and fever, but lesser respiratory involvement than in the first five waves.

We believe this study will help to improve understanding, to monitor trends, to identify possible risk and protective factors and to better develop policies, recommendations and practices designed to reduce transmission, morbidity and mortality among pediatric patients with CF.

As information about SARS-CoV-2 infection continues to evolve, there remains much to be understood about its impact on cwCF. Therefore, continued surveillance and additional research on cwCF will be required to confirm our results.

AUTHOR CONTRIBUTIONS

Pedro Mondejar-Lopez: Investigation; writing—original draft; conceptualization; methodology; validation; visualization; writing—review and editing; formal analysis; project administration; data curation; supervision; resources; software. **Laura Moreno-Galarraga**: Conceptualization; investigation; writing—original draft; methodology; writing—review and editing; resources. **Enrique Blitz-Castro**: Writing—original draft; writing—review and editing. **Maynor Bravo-Lopez**: Resources. **Silvia Gartner**: Resources. **Estela Perez Ruiz**: Resources. **Pilar Caro-Aguilera**: Resources. **Veronica Sanz-Santiago**: Resources. **Alejandro Lopez-Neyra**: Resources. **Carmen Luna-Paredes**: Resources. **Miguel Garcia-Gonzalez**: Resources. **Jordi Costa-Colomer**: Resources. **Maria Cols-Roig**: Resources. **Isabel Delgado-Pecellin**: Resources. **Silvia Castillo-Corullon**: Resources. **Marta Ruiz de Valbuena-Maiz**: Resources. **Patricia W. Garcia-Marcos**: Resources; investigation. **Antonio J. Aguilar-Fernandez**: Resources. **Carlos Martin-De Vicente**: Resources. **Mª Verisima Barajas-Sanchez**: Resources. **Orlando Mesa-Medina**: Resources. **Catalina Bover-Bauza**: Resources. **Joan Figuerola-Mulet**: Resources. **Belen Garcia-Aviles**: Resources. **Carlos Garcia-Magan**: Resources. **Patricia Juarez-Marruecos**: Resources. **Jose Ramon Gutierrez-Martinez**: Resources. **Isidoro Cortell-Aznar**: Resources. **David Gomez-Pastrana**: Resources. **M. Valle Velasco-Gonzalez**: Resources. **M. Isabel Barrio**: Resources. **Manuel Sanchez-Solis**: Resources; investigation. **Oscar Asensio de la Cruz**: Resources; visualization. **Maria Dolores Pastor-Vivero**: Conceptualization; investigation; writing—original draft; writing—review and editing; validation; visualization; methodology; formal analysis; project administration; data curation; supervision; resources.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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