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Impact of SARS-CoV-2 infection in patients with cystic fibrosis in Spain: Incidence and results of the national CF-COVID19-Spain survey

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ARTICLE INFO

Keywords:
Cystic fibrosis
SARS-CoV-2
Coronavirus
COVID-19

ABSTRACT

Background: Given the high incidence of confirmed infection by SARS-CoV-2 and mortality by COVID-19 in the Spanish population, its impact was analysed among persons with Cystic Fibrosis (CF) as a group at risk of a worse evolution. The possible causes of the incidence observed in them are explained and how CF Units have faced this health challenge is detailed.

Methods: Retrospective descriptive observational study, for which a Spanish CF Patients with Confirmed COVID-19 Registry is created, requesting information on number of people affected between 8 March–16 May 2020 and their clinical-demographic characteristics from the CF Units participating in the *European Cystic Fibrosis Society Patient Registry* (ECFSPR). The accumulated incidence is calculated, compared with that of the general population. Additionally, a survey (CF-COVID19-Spain) is carried out on prevention of SARS-CoV-2 infection, workings of CF Units and possible reasons for the incidence observed.

Results: COVID-19 was diagnosed in eight CF patients, one of whom had received a lung transplant. The accumulated incidence was 32/10000 in CF patients and 49/10000 in the general population. General death rate was

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5.85/10000 while no CF patients included in the ECFSPR died. The characteristics of those affected and the results of the survey are described.

Conclusions: Despite being considered a disease at high risk of severe COVID-19, the low incidence and mortality in CF patients in Spain contrasts with the figures for the general population. The possible factors that would explain such findings are discussed, with the help of the results of the CF-COVID19-Spain survey.

1. Introduction

On 7 January 2020, health officials in China announced that they had identified a novel coronavirus in patients with pneumonia in Wuhan (Hubei province) [1]. The first cases shared the fact that they had recently visited the Huanan wholesale seafood market, in that city. The new virus, denominated SARS-CoV-2, constitutes the seventh member of the coronavirus family that infects humans. On 11 February 2020, the World Health Organization (WHO) gave the new disease caused by this virus the acronym of COVID-19, from *CO*rona*VI*rus *D*isease – 2019. The virus spread rapidly, and therefore the WHO officially declared the pandemic by SARS-CoV-2 on 11/03/2020 [2]. Its high transmissibility and pathogenicity have led to more than 4.5 million people being infected and 300000 deaths in 190 countries [3].

The pandemic is having a major impact in Spain, with higher morbidity and mortality in elderly persons or those with certain underlying pathologies. Following the government decreeing lockdown of the population on 14/03/2020, the peak in the daily numbers of people infected and deaths was reached in late March and early April 2020, after which a slow progressive drop in the rates of accumulated incidence (AI) and mortality was achieved. With 230698 cases confirmed by PCR (*Polymerase Chain Reaction*), Spain is currently the second most affected country, after United States; with the most cases per capita (49/10000); most total deaths (27561) behind United States, United Kingdom, Italy and France; and most deceased per capita (5.85/10000) after Belgium [3,4].

Cystic fibrosis (CF) is a hereditary, multi-systemic disease and with limited life expectancy, caused by mutations in the gene CFTR. Its incidence in newborns is calculated at 1/2500–5000 and it is more prevalent in Caucasians [5]. Numerous national and international protocols and guidelines have appeared since March 2020 on the management of patients affected by COVID-19, all of which include children and adults with CF among the groups at risk of a worse evolution [6,7]. To date, little is known about the impact and consequences of infection by SARS-CoV-2 in persons with CF [8]. Recently, the ‘*Cystic Fibrosis Registry Global Harmonization Group*’ published a series of 40 CF patients with COVID-19 in eight countries [9].

In the light of the high incidence and mortality by COVID-19 in Spain, we proposed a double objective. On the one hand, to determine the incidence of infection by the novel coronavirus and the impact of the first ten weeks of pandemic on the cohort of persons with CF as a possible population at risk of severe COVID-19. On the other hand, to detail how Spanish CF Units have dealt with this health challenge for the purposes of adequate prevention of infection by the novel coronavirus, how clinical monitoring has been maintained, and how to explain the incidence observed in this group of patients.

2. Methods

This was a retrospective descriptive observational study in which all the CF Units in Spain participating in the ECFSPR were contacted with the two main aims detailed below.

2.1. Series of cases and incidence in CF patients in Spain

At the instances of the *Spanish Cystic Fibrosis Society* a registry was established of Spanish CF patients with infection due to SARS-CoV-2 confirmed by means of PCR, and which includes the following

anonymous data: gender, age, CF genotype, body mass index, predicted baseline FEV₁, microbiology, azithromycin intake, pancreatic involvement, need for admission to hospital and/or the Intensive Care Unit (ICU), lung transplant, treatment received and evolution. Cases were identified as people with a confirmed diagnosis of CF who tested positive for SARS-CoV-2 PCR between 8 March – 16 May 2020 and who were included in the ECFSPR. Therefore, both in CF patients as well as in the general population, cases that were suspected but not confirmed by PCR or not tested due to low suspicion or mild symptoms were excluded, as were CF patients belonging to the few Spanish CF Units that still do not participate in the ECFSPR. After receiving regulatory permission, a request was made to the Spanish Coordinator of the registry for data referring to the preliminary number of Spanish CF patients included in 2018 and whose report is to be published shortly [10]. According to the registry, there were 2498 patients in Spain at the end of 2018 (estimated coverage 90%), 212 of whom had received lung transplants (‘personal communication’). The AI of COVID-19 was calculated in CF and in the whole population of Spain which, according to the latest census from the National Statistics Institute (1 July 2019), totalled 47100396 inhabitants [4,11].

2.2. FQ-COVID19-Spain survey to CF units

A survey consisting of eight questions with unbounded answers was sent to those Spanish CF units participating in the ECFSPR as well as to the few that still do not participate in it and to secondary CF units or those associated to reference units. Our main aims were to know their opinions in relation with the prevention of the infection in their patients and the possible causes of the AI observed.

2.3. Ethical issues

All patients included in ECFSPR had a signed informed consent for participating in it. Registration was carried out according to Spanish Laws 14/2007 on Biomedical Research and 15/1999 on the Protection of Personal Data.

3. Results

3.1. Series of cases and incidence in CF patients in Spain

In the study period, eight cases of COVID-19 were notified in CF patients, four in females and four in males, median age of 32.5 years (range 7–45 years), two of them <18 years old (Table 1). All eight had fever and respiratory symptoms when diagnosed. Four were homozygotes F508del, three heterozygotes F508del and one had a genotype with a residual function mutation; 62.5% had pancreatic insufficiency, 37.5% CF-Related Diabetes (CFRD) and 75% chronic bacterial pulmonary infection, of which 83% were due to *Pseudomonas aeruginosa*, 37.5% *Staphylococcus aureus* and 12.5% *Burkholderia cepacia* or *Stenotrophomonas maltophilia*. Among the non-transplanted cases, median baseline predicted FEV₁ was 68% (range 39–90%). Both paediatric cases were infected healthcare workers’ children and the only ones not admitted to hospital, since they had short-term mild symptoms and did not require specific treatment for the infection. All the adults required hospitalisation, with four from six needing supplementary oxygen, although none required mechanical ventilation. One patient had undergone lung transplantation two years before, had a baseline FEV₁ of

88% and was on tacrolimus and mycophenolate mofetil therapy; this was the only one who was admitted to the ICU. Table 2 describes pharmacological treatments and outcomes.

On 16/05/2020, the AI of confirmed infection in CF patients was 32/10000 patients, lower than that detected in the general population in Spain (49/10000 inhabitants). The mortality rate for COVID-19 was 5.85/10000 inhabitants in Spain while no deaths have been recorded to date among CF patients included in the *ECFSPR*. It should be noted that, in addition to the cases described, the authors have knowledge of another adult Spanish patient, who received a lung transplant 10 years ago, not notified and not included in the *ECFSPR*, who died due to complications derived from COVID-19 ('personal communication').

3.2. CF-COVID19-Spain survey in CF units

The survey was sent to 39 Spanish specialists in adult or pediatric CF and Pulmonology, all of them coordinators and major responsible persons of their CF units. Answers were received from 30 doctors (77% of the total). The answers to questions on the prevention of COVID-19 in CF patients and the measures implemented by the Spanish CF units are summarised in Table 3.

4. Discussion

In a brief timespan, numerous publications on COVID-19 have become available, although very few are specific with regard to CF. A recently published multinational report includes 40 CF patients with SARS-CoV-2 infection [9], but excludes cases in those European countries with the highest incidence and mortality by COVID-19 to date, i.e., Spain and Italy [3]. The intensity of the SARS-CoV-2 pandemic in Spain has reached enormous proportions. However, it would appear that it has not, thus far, been as virulent in CF patients. Even though, supposedly, they are more susceptible to suffering from severe COVID-19 should they become infected and if the infection is confirmed in the event of clinical suspicion, the AI in them is lower than in the general population (32 vs. 49/10000 persons). Although Cosgriff's article main aim was not to report the AI of SARS-CoV-2 infection in every participating country, it informed of a global AI of 7 vs. 15/10000 between 1 February and 13 April 2020 [9], being both figures lower than the Spanish ones. However, the AI of COVID-19 in the western countries included in said report (USA, UK, France, Canada, Netherlands, Ireland) could be underestimated due to it being carried out in the initial stages of the pandemic, since the AI was very low and even absent until mid-March 2020 and followed a clear increase until April 13 (end of cases recruitment). Those same authors refer that the different phases of the pandemic that each country was experiencing when the study was undertaken is a limitation. Conversely, on 16/05/2020, the relatively low number of cases and deaths due to COVID-19 in Spain had led to the start of easing lockdown, which could better reflect the homogeneity of the AI in the first ten and most critical weeks of the pandemic. No Spanish CF patient included in the *ECFSPR* has died, in contrast to a mortality rate of 5.85/10000 and a case fatality rate of 11.9% in non-CF patients. These findings are comparable to those published by Cosgriff R et al. [9].

The CF patients with confirmed COVID-19 in Spain have been mostly adults with mild-moderate clinical expression and an excellent evolution, even though four of them had moderate-severe lung affection (baseline FEV₁ 39–66%). All were symptomatic in contrast to Cosgriff's cohort [9], in which 11 CF patients (22.5%) were tested for SARS-CoV-2 in the absence of symptoms. The different AI found in different countries could highly depend on various testing strategies. According to the COVID-CF project in Europe, 50% CF patients who tested positive for the new coronavirus were asymptomatic [12]. CF-COVID-Spain survey reveals that asymptomatic Spanish patients were never tested for the virus during the study period. Although due to the fact that the only transplanted patient required admittance to the ICU definitive conclusions cannot be reached, it is possible that the condition of

immunosuppression is an added and even greater risk factor for an unfavourable evolution than CF itself. The death of a transplanted CF patient not included in the *ECFSPR* would also support this hypothesis. Unlike Spanish cohort, post-transplant patients with CF may be over-represented in Cosgriff's one (27.5%). Authors explain the higher proportion (91%) of post-transplant patients tested by a specific monitoring protocol in lung transplant centers.

The low detection of infections in minors with CF should be highlighted, even though it is a potentially serious paediatric disease. Affected Spanish paediatric CF patients were infected healthcare professionals' children, being this fact a logical risk factor for the infection. Likewise, mention should be made of the low incidence and absence of mortality in adults with CF, who, in general, have more advanced lung disease than children. In the absence of enough scientific evidence, we consider that several possible causes can explain these findings, some of which are extracted from the CF-COVID19-Spain survey.

One of the factors that explains the low incidence of infection by SARS-CoV-2 in persons with CF is probably the well contrasted habit of the steps they take to prevent respiratory infections [13], such as the use of face masks and hydroalcoholic disinfectant gel, frequent hand-washing, social distancing at 2 m and avoiding crowded public places.

Likewise, 47% of the doctors questioned referred to the fact that many patients subjected themselves to home isolation as a preventive measure in late February-early March 2020 before the official lockdown on 14/03/2020. Furthermore, some children with CF stopped attending school or day-care prior to the said decree (stated by 37% of paediatric units), some of their parents requested medical reports on their children in order to be able to work remotely or remain at home (60% of paediatric units) and some adults with CF asked for medical reports in order to be able to work remotely or obtain medical leave (27% of adult units). We consider that this early and stricter confinement to be a key factor in explaining the low incidence detected in CF patients.

According to data from the Spanish Ministry for Health and the Instituto de Salud Carlos III [4], 70% of the cases notified in Spain were in persons over 50 years old and 87% of those who died were aged over 70 years, which puts age as the main risk factor for severe COVID-19. Conversely, according to the *ECFSPR* in 2017 [14], the median age of Spanish CF patients was 17 years, 47.5% were adults and only 24% were over 30 years old. In our series of COVID-19 cases in CF, the median age is much higher (32.5 years) and similar to the 33 years reported by Cosgriff R et al. [9]. The lower mean age of CF population could act as a protective factor against an unfavourable evolution. The paucisymptomatic presentation observed in children [15], both in those with an underlying pathology as well as without, together with the consequent fewer PCR tests carried out in mild cases, supports this hypothesis. In fact, the 0–14 years age group represents only 0.6% of the total number of notified cases in Spain [4].

Several hypotheses would explain the low incidence and pathogenicity of the virus in the paediatric population. It has been shown that the angiotensin-converting enzyme 2 (ACE2) acts as a cellular receptor for SARS-CoV-2 [16], thus the higher the expression of ACE2 the worse the evolution of the tissue damage that it causes. It is speculated that children have milder forms of the disease because the maturity and function (e.g. capacity to bond to receptor) of ACE2 is lower than in adults. This and other factors observed in the paediatric population, such as a greater activation and training of innate immunity due to frequent viral infections (including other coronaviruses) and vaccinations, the higher physiological counts of B/T lymphocytes and NK cells with respect to adults [17], and the absence of endothelial damage in healthy children, which has been involved in the inflammatory response to the virus, could at least partially explain the mildness observed at this age [18].

In the same sense, we could propose thick respiratory secretions, their respiratory microbiota and the virus-bacteria interaction in their lungs as being protective factors in patients with CF. Shi and Gewirtz

Table 1

Clinical and demographic characteristics of CF patients diagnosed in Spain since the start of the pandemic (8 March-16 May 2020).

Case	Age (years)	Gender	CF Genotype	BMI	FEV ₁	Chronic Infection	Azithromycin Intake	Pancreatic involvement	Lung Transplant
1	7	Male	F508del/L206W	17.82	–	-	NO	PS	NO
2	17	Male	F508del/F508del ^a	19.77	79%	<i>P. aeruginosa</i> <i>S. Aureus</i>	YES	PI	NO
3	24	Female	F508del/G542X	22.66	90%	<i>P. Aeruginosa</i> <i>S. Aureus</i> <i>S. Maltophilia</i>	NO	CFRD, PI	NO
4	27	Male	F508del/F508del	22.74	61%	<i>P. Aeruginosa</i>	YES	PI	NO
5	38	Male	F508del/F508del	23.3	88%	-	YES	CFRD, PI	YES
6	42	Female	N1303K/3272-26A > G	23.34	66%	<i>S. Aureus</i> <i>B. Cepacia</i>	NO	PS	NO
7	44	Female	F508del/F508del	23.24	39%	<i>P. Aeruginosa</i>	YES	CFRD, PI	NO
8	45	Female	F508del/E528E	28.08	55%	<i>P. Aeruginosa</i>	YES	PS	NO

BMI: body mass index (kg/m²); FEV₁%; forced expiratory volume in first second (percentage of predicted), according to *Global Lung Function Initiative* (GLI); CFRD: Cystic Fibrosis-Related Diabetes; PS: pancreatic sufficiency; PI: pancreatic insufficiency.

^a Reported as using tezacaftor/ivacaftor therapy.

Table 2

Hospitalisation, treatment and outcomes.

	n	%
Hospitalisation	6	75
Intensive care unit	1	12,5
Supplemental oxygen	4	50
Non-invasive or invasive mechanical ventilation	0	0
Azithromycin	5	62,5
Hydroxychloroquine	6	75
Lopinavir/Ritonavir	4	50
Tocilizumab	1	12,5
Systemic antibiotics	7	87,6
Systemic corticosteroids	3	37,5
Recovered	8	100
Died	0	0

reviewed this topic in 2018, suggesting that different bacteria could inhibit virus infections, reducing their infectability or activating the immune system [19]. However, this has not been specifically proven in CF.

Up to 95% of deaths in Spain occurred in people with at least one underlying disease [4]. Retrospective analyses reflect that male sex [20–22], age > 65 [20–24] and certain chronic conditions such as arterial hypertension (AHT) [20,22,25–27], diabetes mellitus (DM) [20–23,27], cardiovascular disease (CVD) [21,22,24,26], cerebrovascular disease [21,24,27] or cancer [21,27] are the most relevant independent risk factors for worse evolution or mortality. A recent meta-analysis shows that AHT (16%), CVD (12.1%), DM (7.87%), smoking (7.63%), chronic obstructive pulmonary disease (COPD) (0.95%), cancer (0.92%) and chronic kidney disease (0.83%) were the most prevalent underlying pathologies among 76993 patients hospitalised for COVID-19 [28]. Contrary to what would be expected, the most prevalent chronic respiratory diseases are not among the main factors affecting severity in the majority of the published series [21], with no scientific evidence available to explain this finding [29]. Li X et al. [22] published a series of 548 persons hospitalised for COVID-19 in Wuhan, of whom 3.1% and 0.9% had COPD and asthma, respectively, as opposed to 30.3%, 15.1%, 6.2% or 4.7% with AHT, DM, CVD or cancer, respectively. However, Guan W et al. [27] conferred COPD a relative risk of severity or mortality of 2.68 (95%CI 1.42–5.05; p = 0.002) after analysing 1590 patients, although only 24 of them (1.5%) suffered from said pathology, in contrast with 53.7%, 16.9% or 8.2% who had CVD, AHT or DM, respectively. It should be highlighted that 50% of the adults in our series had CFRD under treatment with insulin, in contrast to a lower reported CFRD prevalence (26%) among adults in *ECFSPR* 2017. This could have acted as a proinflammatory risk factor and for added microvascular affection.

Obesity [30] and smoking [31], which increases ACE2 expression,

are associated with more severe forms of COVID-19; both conditions are less prevalent in CF patients, so they would be protected in this sense against said severe clinical presentations. The mean BMI of adults in this COVID-19 cohort was 23.9 kg/m², which is higher than in the adult CF Spanish population as a whole (22.3 kg/m²). This could have acted as an additional risk factor for the disease.

Although there are no randomised clinical trials that support the use of azithromycin in COVID-19, it has been widely used in combination with hydroxychloroquine [32,33] due to their immunomodulatory and antiviral properties, the latter only demonstrated *in vitro* [34]. Forty-four percent of the doctors surveyed considered that the chronic treatment with azithromycin received by many CF patients could act as a protective factor against SARS-CoV-2.

It is deduced from the CF-COVID19-Spain survey that, in the initial phase of the pandemic, the face-to-face routine monitoring of CF patients was substituted by telemedicine. Two out of every three doctors expressed that their patients demanded less health attention and/or had fewer respiratory exacerbations than prior to the pandemic. All the above, coupled with less spirometry or routine respiratory secretion cultures, could have negative consequences in the short-medium term in patients who require close monitoring, such as an undetected and irreversible fall in lung function, untreated silent primary bacterial infection (i.e. *Pseudomonas aeruginosa*), increase in the fear of respiratory pathogens, or a greater prevalence of anxiety and depression.

4.1. Limitations

The low number of CF patients with confirmed COVID-19 precludes the extraction of definitive conclusions. We are facing a pandemic that has yet to run its course and the accumulated data may change in the short term. As not all the Spanish CF patients are included in the *ECFSPR*, we cannot provide a totally accurate AI, but one which is very close to the real picture. In addition, Spanish CF Units generally followed restrictive testing strategies that could have resulted in an underestimated AI of the viral infection. The PCR tests may give some false negatives for SARS-CoV-2 [35] and there will be mild or asymptomatic cases that have not been tested, which occurs in both the general population as well as in the CF patients.

5. Conclusions

Even though CF is a health risk for severe COVID-19, none of the non-transplanted patients and included in the *ECFSPR* has died, and the AI seems apparently low compared to the general population. In contrast, lung transplant-related immunosuppression could act as an additional risk factor for mortality in CF patients. The CF-COVID19-Spain survey, with questions open to expert comments, has served to help deduce the possible multifactorial causes which could explain that low incidence

Table 3
CF-COVID19-Spain survey results.

Questions	Answers	%
1. In which cases have you tested CF patients for SARS-CoV-2 in your unit?	a) There has not been a need to test.	33
	b) If symptoms are suggestive of COVID-19	37
	c) If moderate-severe respiratory exacerbation	23
	d) Only if admitted to hospital	7
2. When did some or all of the CF patients from your unit begin home confinement?	a) Late February – early March 2020, before the official lockdown decree.	47
	b) Day of the official lockdown decree (14/03/2020)	40
	c) Do not know/No answer	13
3. Do you believe that the chronic treatment with azithromycin that many patients with CF receive may have had a protective role against the infection?	a) Definitely yes	27
	b) Probably	17
	c) "I have my doubts"	17
	d) Little experience in children with chronic azithromycin ^a	13
	e) Do not know/No answer ^a	26
4. Do you believe that children with CF are experiencing asymptomatic/ oligosymptomatic forms of the infection?	a) Yes	53
	b) Do not know/No answer ^b	47
5. Are your patients demanding more or less health care attention during the pandemic lockdown than they usually demand?	a) More attention than before	0
	b) The same attention as before	20
	c) Less attention than before	67
	d) Do not know/No answer	13
6. Does your unit continue to routinely conduct sputum cultures or throat swabs?	a) No or only if respiratory exacerbation	60
	b) Yes, the samples are brought by a relative	17
	c) Do not know/No answer	23
7. How are your CF patients getting their usual medication during the pandemic lockdown?	a) By courier from Hospital Pharmacy	60
	b) Collected by a relative	27
	c) Regional CF patients' association	7
	d) Do not know/No answer	6
8. Have you carried out any modality of telemedicine applied to your CF patients during the lockdown?	Scheduled visits:	
	a) Telephone visits on the day scheduled	53
	b) No scheduled visits (only if necessary)	44
	c) Visits in person as always	3
	Non-scheduled attention (one or more of the following):	
	a) Using clinic's telephone	97
	b) By email	67
c) Using doctor's private telephone	30	

Apart from the answers, the doctors surveyed added useful comments in order to seek to explain the low incidence rate of COVID-19 in CF patients in Spain.

^a Answers mainly by paediatricians.

^b Answer mainly by doctors for adults.

observed, although they are all hypothetical and will require further study in the future as the pandemic advances and we better understand the long-term impact of infection by SARS-CoV-2 in persons with CF.

Declaration of competing interest

The authors have no conflicts of interest to declare relating to this work.

CRediT authorship contribution statement

Pedro Mondejar-Lopez: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing - original draft, Writing - review & editing. **Esther Quintana-Gallego:** Conceptualization, Investigation, Methodology, Project administration, Visualization, Writing - review & editing.

Rosa M. Giron-Moreno: Resources. **Isidoro Cortell-Aznar:** Resources. **Marta Ruiz de Valbuena-Maiz:** Resources. **Layla Diab-Caceres:** Resources. **Concepcion Prados-Sanchez:** Resources. **Antonio Alvarez-Fernandez:** Resources. **Patricia W. Garcia-Marcos:** Conceptualization, Formal analysis. **Carlos Peñalver-Mellado:** Data curation, Investigation. **M. Dolores Pastor-Vivero:** Data curation, Project administration, Resources. **Casilda Oliveira:** Resources. **Alejandro Lopez-Neyra:** Conceptualization, Visualization. **Silvia Castillo-Corullon:** Conceptualization, Visualization. **Samara Palma-Milla:** Conceptualization, Visualization. **Estela Perez-Ruiz:** Conceptualization, Visualization. **Amparo Sole-Jover:** Conceptualization, Visualization. **M. Isabel Barrio:** Conceptualization, Investigation, Visualization. **Manuel Sanchez-Solis:** Conceptualization, Formal analysis, Methodology, Supervision, Validation, Writing - review & editing. **Óscar Asensio de la Cruz:** Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing - review & editing.

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